

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 31/445, C07D 211/30 C07D 211/20		A1	(11) International Publication Number: WO 91/03243 (43) International Publication Date: 21 March 1991 (21.03.91)
(21) International Application Number: PCT/US90/04850		(74) Agents: HORN, Margaret, A. et al.; E.I. du Pont de Nemours and Company, Legal Department, 1007 Market Street, Wilmington, DE 19898 (US).	
(22) International Filing Date: 30 August 1990 (30.08.90)			
(30) Priority data: 404,813 8 September 1989 (08.09.89) US 570,199 20 August 1990 (20.08.90) US		(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent)*, DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), HU, IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent), SU.	
(71) Applicant: E.I. DU PONT DE NEMOURS AND COMPANY [US/US]; 1007 Market Street, Wilmington, DE 19898 (US).		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(72) Inventors: CAIN, Gary, Avonn ; 80 Freedom Trail, New Castel, DE 19720 (US). GILLIGAN, Paul, Joseph ; 773 Montclair Drive, Claymont, DE 19703 (US). TAM, Sang, William ; 443 Stella Drive, Hockessin, DE 19707 (US).			
(54) Title: ANTIPSYCHOTIC 1-CYCLOALKYLPIPERIDINES			
(57) Abstract There are provided cycloalkyl piperidine compounds which are useful in the treatment of physiological or drug-induced psychosis or dyskinesia in a mammal. These novel compounds are selective sigma receptor antagonists and have a low potential for movement disorder side effects associated with typical antipsychotic agents.			

* See back of page

DESIGNATIONS OF "DE"

Until further notice, any designation of "DE" in any international application whose international filing date is prior to October 3, 1990, shall have effect in the territory of the Federal Republic of Germany with the exception of the territory of the former German Democratic Republic.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT Austria	ES Spain	MC Monaco
AU Australia	FI Finland	MG Madagascar
BB Barbados	FR France	ML Mali
BE Belgium	GA Gabon	MR Mauritania
BF Burkina Faso	GB United Kingdom	MW Malawi
BG Bulgaria	GR Greece	NL Netherlands
BJ Benin	HU Hungary	NO Norway
BR Brazil	IT Italy	PL Poland
CA Canada	JP Japan	RO Romania
CF Central African Republic	KP Democratic People's Republic of Korea	SD Sudan
CG Congo	KR Republic of Korea	SE Sweden
CH Switzerland	LJ Liechtenstein	SN Senegal
CM Cameroon	LK Sri Lanka	SU Soviet Union
DE Germany	LU Luxembourg	TD Chad
DK Denmark		TC Togo
		US United States of America

TitleAntipsychotic 1-CycloalkylpiperidinesRelated Application

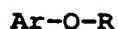
5 This application is a continuation-in-part of my copending U.S. Application Serial No. 07/404,813, filed September 8, 1989.

Field of the Invention

10 This invention relates to novel cycloalkyl-piperidine compounds, pharmaceutical compositions containing them and methods of using these compounds to treat physiological or drug induced psychosis and as antidyskinetic agents.

Background of the Invention

15 U.S. Patent No. 4,225,608 (Uhl et al.) discloses phenoxyalkylamines of the formula:



wherein:

20 Ar is phenyl optionally substituted with 1 or 2 substituents selected from the group: F, Cl, Br, alkyl or alkoxy each of 1 to 4 carbon atoms, cycloalkoxy of 3 to 6 carbon atoms, CF_3 , CN, alkylthio of 1 to 4 carbon atoms, SCF_3 , OH or

25 alkanoyloxy of 1 to 10 carbon atoms; R is $(1-\text{R}^1-2\text{-pyrrolidyl})-\text{CH}_2-\text{CHR}^2-$, $(1-\text{R}^1-2\text{-piperidyl})-\text{CH}_2-\text{CHR}^2-$ or $1-\text{R}^1-3\text{-Z-4-hexahydroazepinyl}$;

30 R^1 is H, alkyl or alkenyl each of up to 4 carbon atoms, cyclopropylmethyl or benzyl;

R^2 is H, alkyl of 1 to 4 carbon atoms or phenyl; and

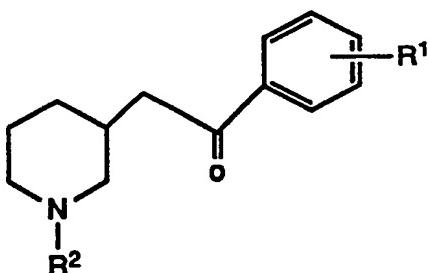
35 Z is alkyl of 1 to 4 carbon atoms with the proviso that Ar is p-fluorophenyl only if R is not $2-(1\text{-methyl-2-piperidyl})\text{-ethyl}$.

2

The phenoxyalkylamine compounds have antidepressant activity.

Japanese patent 48-40779 (Dainippon) describes the process for preparing compounds of the formula:

5



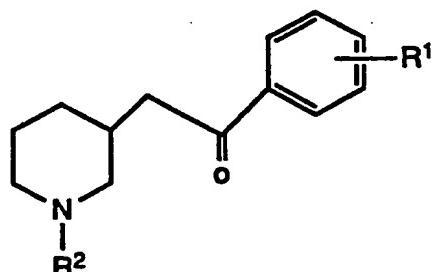
wherein:

R¹ is H, halogen, alkyl, alkoxy or trihalomethyl;
and

10 R² is alkyl, alkenyl, hydroxyalkyl,
cycloalkylalkyl, dimethylaminoalkyl, aralkyl,
arylalkenyl, arylalkoxy, aryloxyalkyl, 2-
halophenothenothiazinyl(10)-propyl, 10, 11-dihydro-
5H-dibenzo (b,f)azepin-5-yl-propyl or 3-halo-
15 10,11-dihydro-5H-dibenzo (b,f)azepinyl propyl.

These compounds are described as being useful as pharmaceuticals since they exhibit psychotropic effects, however, no utility is actually documented.

20 Nagai et al. (Dainippon) describe psychotropic compounds of the formula:



wherein:

R¹ is H, Cl or F; and

R² is alkyl, alkenyl, benzyl, phenethyl, hydroxyethyl, cyclopropylmethyl or substituted phenylalkyl.

See: Chemical Pharmaceutical Bulletin 25(8) 1911-1922
5 (1979).

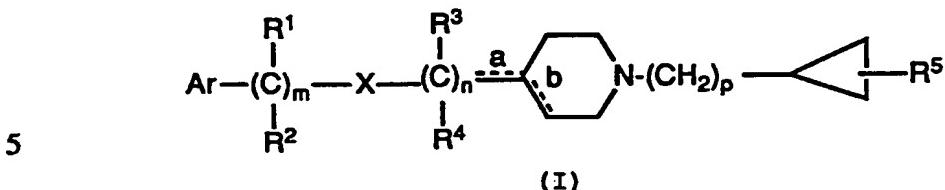
The 3-isomers described in Japanese Patent 48-40779 and in the Chemical Pharmaceutical Bulletin, cited above, do not show the sigma receptor selectivity demonstrated by the compounds of the present invention.

- 10 It is this sigma receptor selectivity of the compounds of the present invention which makes them so advantageous over the compounds in the prior art. Traditionally, antipsychotic agents have been potent dopamine receptor antagonists. For example,
- 15 phenothiazines such as chlorpromazine and most butyrophenones such as haloperidol are potent dopamine receptor antagonists. These dopamine receptor antagonists are associated with a high incidence of side effects, particularly Parkinson-like motor effects or
- 20 extra-pyramidal side-effects (EPS), and dyskinesias including tardive dyskinesias at high doses. Many of these side effects are not reversible even after the dopamine receptor antagonist agent is discontinued.

- 25 The present invention is related to antipsychotic agents which are selective sigma receptor antagonists rather than the traditional dopamine receptor blockers known in the art, and therefore the compounds of the present invention have low potential for the typical movement disorder side-effects associated with the
- 30 dopamine antagonist antipsychotic agents while they maintain the ability to antagonize aggressive behavior and antagonize hallucinogenic-induced behavior.

Summary of the Invention

The antipsychotic compounds of the present invention are cycloalkylpiperidines of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

m is 0 to 3;

n is 0 to 3;

provided that m and n are not both 0;

p is 0 to 3;

O
"n"

X is O, S, SO, SO₂, NR⁶, CR⁷R⁸, C, or CHO;

R¹, R³ and R⁷ independently are H, alkyl of 1 to 5 carbon atoms, halogen, NR¹⁰R¹¹, OH, CO₂H, carboalkoxy of 2 to 6 carbon atoms, CN, Ar¹, alkoxy of 1 to 5 carbon atoms or alkylthio of 1 to 5 carbon atoms;

R², R⁴ and R⁸ independently are H, alkyl of 1 to 5 carbon atoms, carboalkoxy of 2 to 6 carbon atoms, CN, alkoxy of 1 to 5 carbon atoms or Ar¹;

provided that R¹, R², R³ and R⁴ are not alkoxy of 1 to 5 carbon atoms, alkylthio of 1 to 5 carbon atoms, NR¹⁰R¹¹ or OH when X is O, S, SO, SO₂ or NR⁶;

R⁵ is H, alkyl, halogen, OH or alkenyl;

R⁶ is H, alkyl of 1 to 5 carbon atoms or Ar¹;

Ar and Ar¹ independently are naphthyl, pyridyl, pyrimidyl, indolyl, quinolinyl, isoquinolinyl, or phenyl optionally substituted with

5

alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, haloalkyl of 1 to 3 carbon atoms and 1 to 7 halogen atoms, SH, S(O)_t alkyl of 1 to 3 carbon atoms, where

5 t is 1, 2 or 3, dialkylamino of 2 to 6 carbon atoms, halogen, OH, alkylamino of 1 to 3 carbon atoms, NH₂, CN, NO₂, SO₃H, tetrazole, CO₂H, carboalkoxy of 2 to 6 carbon atoms, CONH₂, SO₂NH₂, COR⁹,

10 CONR¹²R¹³, SO₂NR¹²R¹³, Ar², OAr² or SAR²;

Ar² is naphthyl or phenyl optionally substituted with alkyl of 1 to 3 carbon atoms, haloalkyl of 1 to 3 carbon atoms and 1 to 7 halogen atoms, alkoxy of 1 to 3 carbon atoms, halogen or alkylthio of 1 to 3 carbon atoms;

15 R⁹, R¹⁰, R¹¹, R¹² and R¹³ independently are H, alkyl of 1 to 5 carbon atoms or phenyl or R¹⁰ and R¹¹ taken together are an alkylene chain of 3 to 6 carbon atoms or R¹² and R¹³ taken 20 together are an alkylene chain of 3 to 6 carbon atoms; and
a or b is a double bond or a single bond, provided that both are not double bonds.

Preferred compounds in the present invention are
25 those compounds of Formula (I) wherein:

O
"

X is C, CHO or O; and/or

m is 0; and/or

30 n and p are 1; and/or

R³-R⁵ are H; and/or

Ar is phenyl optionally substituted with halogen, OCH₃, NH₂, NO₂ or another phenyl group.

Specifically preferred compounds of the present
35 invention are:

- a) 1-(cyclopropylmethyl)-4-(2'-(4"-fluorophenyl)-2'-oxoethyl) piperidine
- b) 1-(cyclopropylmethyl)-4-(2'-(4"-fluorophenyl)-2'-oxoethyl) piperidine, hydrobromide salt
- 5 c) 1-(cyclopropylmethyl)-4-(2'-(4"-chlorophenyl)-2'-oxoethyl) piperidine
- d) 1-(cyclopropylmethyl)-4-(2'-(4"-chlorophenyl)-2'-oxoethyl) piperidine, hydrobromide salt
- e) 1-(cyclopropylmethyl)-4-(4'-fluorophenoxyethyl)piperidine
- 10 f) 1-(cyclopropylmethyl)-4-(4'-fluorophenoxyethyl)piperidine, hydrochloride salt
- g) 1-(cyclopropylmethyl)-4-(4'-chlorophenoxy-
- 15 h) 1-(cyclopropylmethyl)-4-(4'-chlorophenoxy-methyl)piperidine, hydrochloride salt
- i) 1-(cyclopropylmethyl)-4-(4'-nitrophenoxyethyl)piperidine
- 20 j) 1-(cyclopropylmethyl)-4-(2'-(4''-biphenyl)-2'-oxoethyl)piperidine
- k) 1-(cyclopropylmethyl)-4-(2'-(4''-biphenyl)-2'-oxoethyl)piperidine, hydrobromide salt.

Also provided in the present invention are pharmaceutical compositions comprising an effective amount of a compound of Formula (I) and a pharmaceutically acceptable carrier.

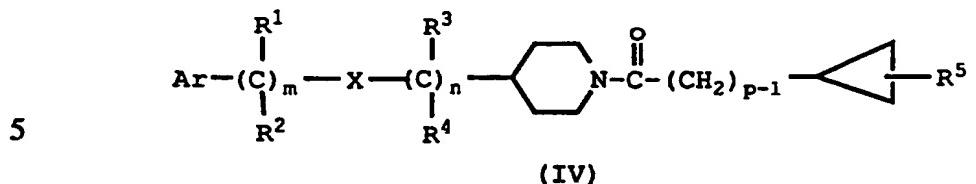
Further provided are methods of using the compounds of Formula (I) for the treatment of physiological or drug-induced psychosis in a mammal as well as for the treatment of dyskinésias in a mammal.

Furthermore, there are provided, processes for the preparation of compounds of Formula (I).

In addition, there are provided novel intermediate compounds and methods of preparing them, useful for the

7

preparation of some of the active compounds of this invention; said intermediate compounds having the formula:



wherein:

m is 0 to 3;

n is 0 to 3;

provided that m and n are not both 0;

p is 1 to 3:

X is O. S. NR⁶:

Ar and Ar^1 independently are naphthyl, pyridyl,

pyrimidyl, quinolinyl, isoquinolinyl or phenyl
optionally substituted with

alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, haloalkyl of 1 to 3 carbon atoms and 1 to 7 halogen atoms, $S(O)_n$ alkyl of 1 to 3 carbon atoms where

t is 1, 2 or 3, dialkylamino of 2 to 6 carbon atoms, halogen, alkylamino of 1 to 3 carbon atoms, CN, NO₂, carboalkoxy of 2 to 6 carbon atoms, COR⁹, CONR¹²R¹³, SO₂NR¹²R¹³, Ar², OAr² or SAR²:

25 Ar² is naphthyl or phenyl optionally substituted with alkyl of 1 to 3 carbon atoms, haloalkyl of 1 to 3 carbon atoms and 1 to 7 halogen atoms, alkoxy of 1 to 3 carbon atoms, halogen or alkylthio of 1 to 3 carbon atoms;

30 R¹-R⁴ and R⁶ independently are H, alkyl of 1 to 5
 carbon atoms or Ar¹;

R^5 is H, alkyl, halogen, OH or alkenyl; and
 R^9 , R^{12} and R^{13} independently are H,

alkyl of 1 to 5 carbon atoms or phenyl, or R¹² and R¹³ taken together are an alkylene chain of 3 to 6 carbon atoms.

5

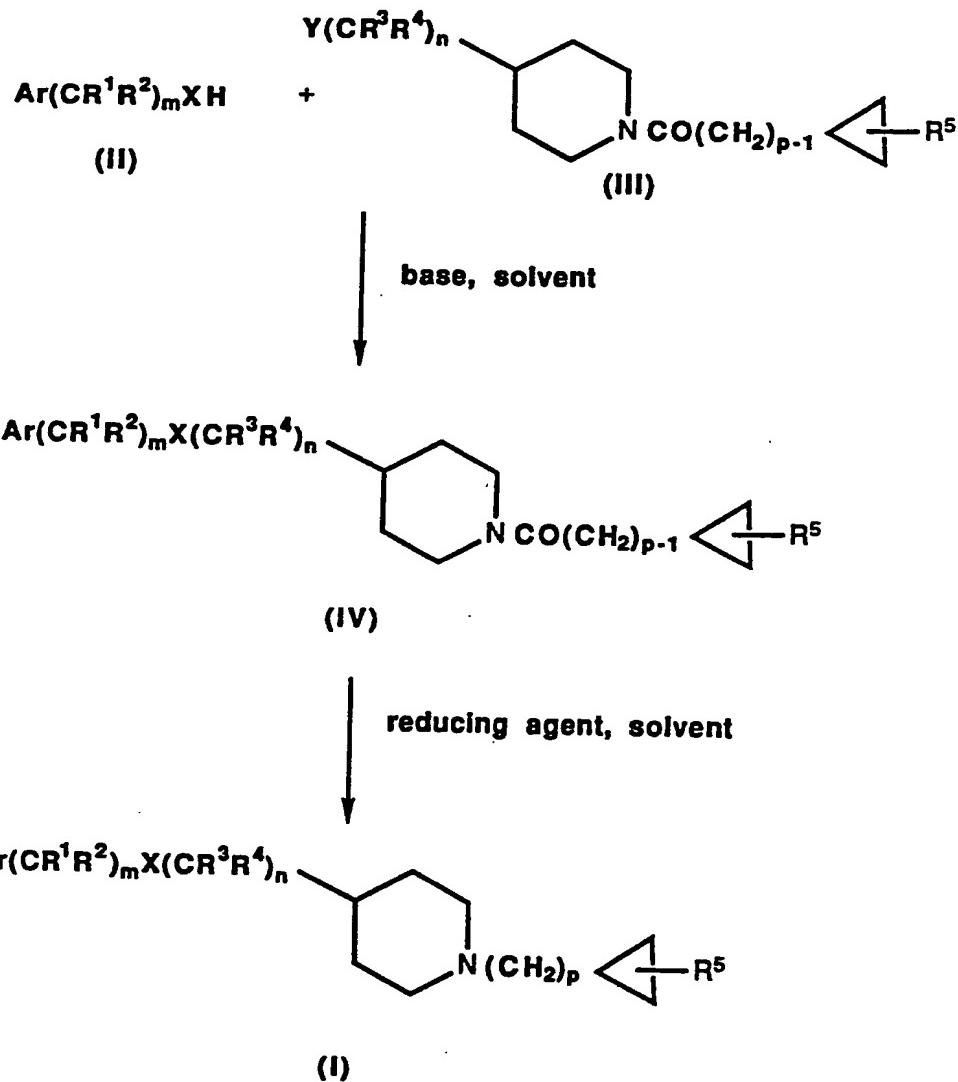
Detailed Description of the Invention

Compounds of Formula (I) may be prepared according to Scheme I. In Scheme I, a compound of Formula (II) [where X is O, S, NR⁶ or CH₂ (when m=1 and CR¹R² = CO) or a single bond (when m=1)] is treated with a base in an inert solvent then reacted with a compound of Formula (III) to afford a compound of Formula (IV). Bases which may be used for this reaction include, but are not limited to, alkali metal hydrides, preferably sodium hydride, alkali metal carbonates, preferably potassium carbonate, alkali metal dialkylamides, preferably lithium di-isopropylamide, alkali metal bis-(trialkylsilyl) amides, preferably sodium bis-(trimethylsilyl)amide, alkyl alkali metal compounds (such as butyl lithium), alkali metal alkoxides (such as sodium ethoxide), alkyl alkaline earth metal halides (such as methyl magnesium bromide), trialkylamines (such as triethylamine or di-isopropylethylamine), polycyclic di-amines (such as 1,4 diazabicyclo [2.2.2]octane or 1,8-diazabicyclo-[5.4.0]undecene) or quaternary ammonium salts (such as Triton B). The choice of inert solvent must be compatible with the choice of base (see J. March, Advanced Organic Chemistry (New York:J. Wiley and Sons, 1985) pp. 255-446; H.O. House, Modern Synthetic Reactions (New York:W.A. Benjamin Inc., 1972, pp. 546-553)). Solvents include lower alkyl alcohols of 1 to 6 carbons, dialkyl ethers of 4 to 10 carbons, cyclic ethers of 4 to 10 carbons, preferably tetrahydrofuran or dioxane, dialkylformamides, preferably N,N-dimethylformamide, dialkylacetamides, preferably N,N-dimethylacetamide, cyclic amides, preferably N-

methylpyrrolidinone, hydrocarbons of 5 to 10 carbons or aromatic hydrocarbons to 6 to 10 carbons. The leaving group Y in Formula (III) may be halide, arylsulfonyloxy, preferably p-toluenesulfonyloxy, alkylsulfonyloxy (such as methanesulfonyloxy), haloalkylsulfonyloxy, preferably trifluoromethylsulfonyloxy or acyloxy, preferably acetoxy. Reaction temperatures range from about -78° to 200°C, preferably about 50-100°C. Compounds of Formula (IV) may be treated with reducing agents in inert solvents to afford compounds of Formula (I). Such reducing agents include but are not limited to, alkali metal aluminum hydrides, preferably lithium aluminum hydride, alkali metal borohydrides, preferably lithium borohydride, alkali metal trialkoxyaluminum hydrides (such as lithium tri-t-butoxyaluminum hydride), dialkylaluminum hydrides (such as di-isobutylaluminum hydride), borane, dialkylboranes (such as di-isoamyl borane), alkali metal trialkylboron hydrides (such as lithium triethylboron hydride). Inert solvents include lower alkyl alcohols of 1 to 6 carbons, ethereal solvents (such as diethyl ether or tetrahydrofuran), aromatic or non-aromatic hydrocarbons of 6 to 10 carbons. Reaction temperatures for the reduction range from about -78° to 200°C, preferably about 50° to 120°C.

The choice of reducing agent and solvent is known to those skilled in the art as taught in the above cited March reference (pp. 1093-1110).

10

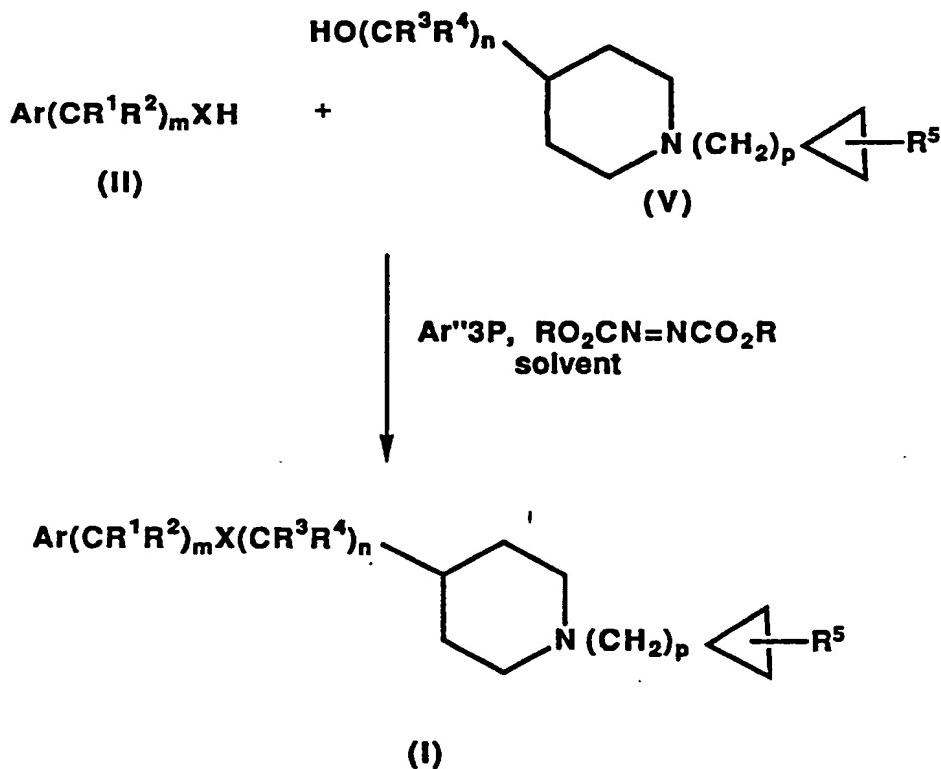
SCHEME I

5 In Scheme II, a compound of Formula (II) ($\text{X} = \text{O}, \text{S}, \text{NR}^6$) is reacted with a compound of Formula (V) in the presence of a triarylphosphine, ($\text{Ar}''\text{3P}$), preferably triphenylphosphine and an azodicarboxylate diester ($\text{RO}_2\text{CN}=\text{NCO}_2\text{R}$) wherein R is lower alkyl, and preferably
 10 diethyl azodicarboxylate in an inert solvent, preferably

11

tetrahydrofuran or benzene. Reaction temperatures range from about 50 to 80°C. The choices of triaryl phosphine, solvent or azodicarboxylate ester are known to those skilled in the art as described by O. Mitsunobu (Synthesis, 1 [1981]).

5

SCHEME II

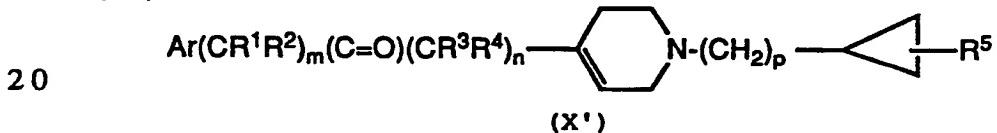
10

In Scheme III a pyridine derivative of Formula (VII) is converted to its metallo derivative (VII*) by treatment with a metallating agent. For the case where n=1 or Y=H, such metallating agents are bases, which 15 include but are not limited to, alkali metal dialkylamides, preferably lithium di-isopropylamide, alkali metal bis(trialkylsilyl)amides, preferably lithium or sodium bis(trimethylsilyl)amides, alkali

metal alkoxides, alkali metal hydrides, alkyl alkaline earth metal halides (such as methyl magnesium bromide). For the cases where n is not equal to 1 or Y is halogen, preferably Cl or Br, metallating agents include alkali metals, such as lithium, alkaline earth metals, such as magnesium, or alkyl lithiums, such as n-butyl lithium. Metallating agents include combinations of one of the above reagents and an inorganic salt such as alkaline earth metal halides or transition metal halides, preferably CuBr, ZnCl₂ or CeCl₃. The metalloc derivative of (VII), i.e. (VII*) may be formed in an inert solvent such as lower alkyl alcohols of 1 to 6 carbons, ethereal solvents, such as tetrahydrofuran or 1,2-dimethoxyethane, or aromatic or non-aromatic hydrocarbons of 6 to 10 carbon atoms. Temperatures for the metallation range from about -80°C to 200°C, preferably about -78° to 70°C. Once the metalloc derivative of (VII), i.e. (VII*) is formed, it is reacted in the same solvent with a compound of Formula (VI) (where R is alkoxy of 1 to 6 carbons or halogen) to afford a compound of Formula (VIII). Reaction temperatures range from about -78° to 70°C, preferably about 0 to 70°C. A compound of Formula (VIII) is then converted to a compound of Formula (X) upon treatment with an alkylating agent of Formula (IX) (Z = halogen, alkylsulfonyloxy, or haloalkylsulfonyloxy). Such alkylation can be conducted with or without an inert solvent. When an inert solvent is used, such solvent may be a lower alkyl alcohol of 1 to 6 carbons, an alkanenitrile, preferably acetonitrile, a halocarbon of 1 to 6 carbons, a dialkylformamide of 2 to 6 carbons, a dialkylacetamide of 3 to 7 carbons or an aromatic or non-aromatic hydrocarbon of 6 to 10 carbons. The intermediate (X) may be isolated upon removal of volatiles, chromatography or crystallization or (X) may

be carried on to the next step in Scheme III if it is hygroscopic. Treatment of a compound of Formula (X) with a reducing agent yields a compound of Formula (I) (where X = CHO or C=O [depending on the reducing

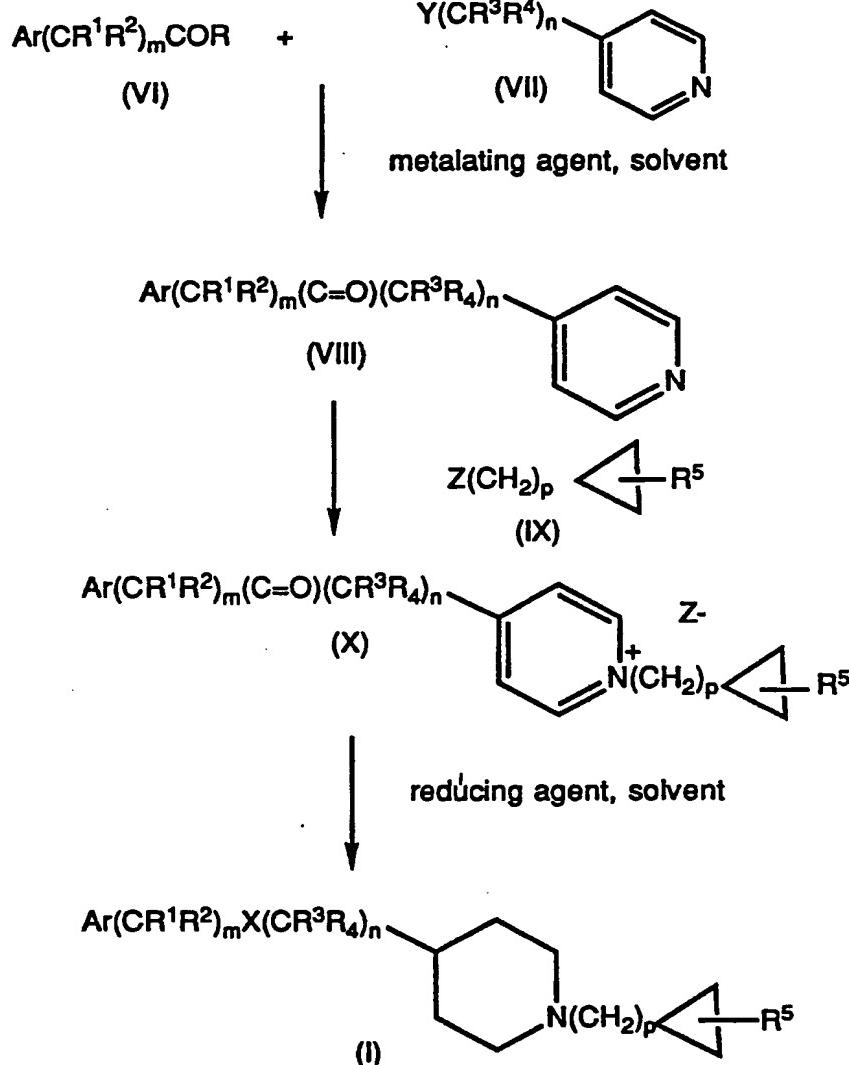
- 5 agent]). Reducing agents include molecular hydrogen and a noble metal catalyst, preferably palladium on carbon or platinum IV oxide, alkali metal aluminum hydrides, preferably lithium aluminum hydride, alkali metal trialkoxyaluminum hydrides, dialkylaluminum hydrides,
- 10 alkali metal borohydrides, preferably sodium borohydride, dialkylboron hydrides, di-imide and its precursors, alkali metal cyanoborohydrides, preferably sodium cyanoborohydride, zinc amalgam or zinc metal. It will be apparent to those skilled in the art that some
- 15 of the above reagents by themselves will only partially reduce the pyridine ring to give tetrahydropyridines among other products (See generally: the above cited March reference, pp. 1093-1110), for example structure (X'):



In these cases, combinations of the above reagents either in tandem or sequentially must be used. Inert solvents include, but are not limited to, lower alkyl

- 25 alcohols, ethereal solvent such as diethyl ether or tetrahydrofuran, aromatic or non-aromatic hydrocarbons of 6 to 10 carbons.

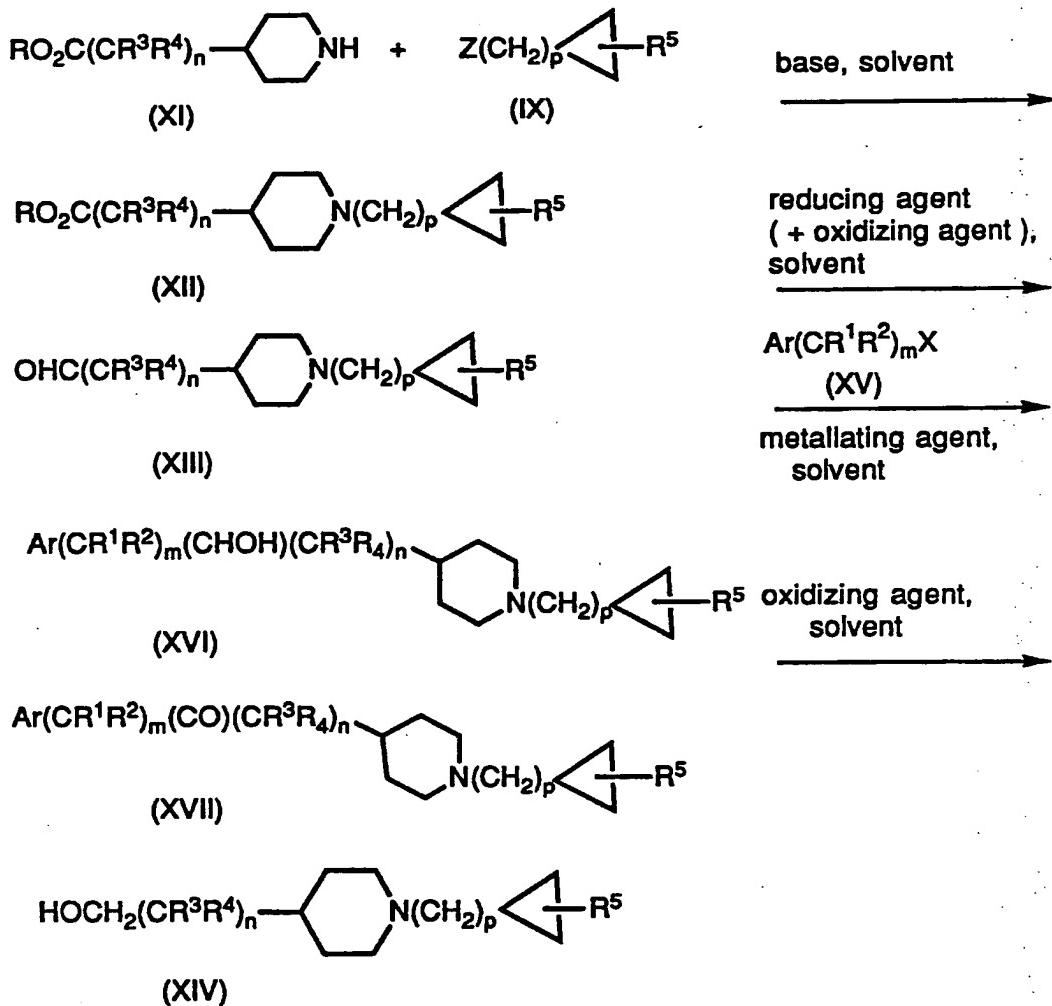
14

SCHEME III

According to Scheme IV, an ester of Formula (XI) (R 5 is alkyl of 1 to 6 carbons or aralkyl of 7 to 10 carbons) is treated with an alkylating agent of Formula (IX) in the presence of a base and an inert solvent. The bases and inert solvents that may be used are the same as those defined for the first reaction step of 10 Scheme I. The resulting ester of Formula (XII) is then

converted to an aldehyde of Formula (XIII) either directly using a reducing agent or indirectly using a reducing agent then an oxidizing agent in sequence. In the latter course, the intermediate alcohol (XIV) may or 5 may not be isolated depending on its stability using standard techniques known to those skilled in the art. Reducing agents and the inert solvents for the reduction include those defined in Schemes I and III. Oxidizing agents for converting an alcohol of Formula (XIV) to an 10 aldehyde of Formula (XIII) include transition metal oxides, such as CrO₃ or MnO₂, pyridine-chromium complexes, such as CrO₃.C₅H₅N, pyridinium dichromate or pyridinium chlorochromate, an oxalylchloride-dimethylsulfoxide-triethylamine reagent system, commonly 15 called the Swern oxidation system (D. Swern et al., J. Organic. Chem., 43, 2480-2482 (1978)) or a dimethyl sulfoxide-dicyclohexylcarbodiimide system (See: H.O. House, Modern Synthetic Reactions (New York:W. A. Benjamin Inc., 1972) pp. 416-421). Such oxidations, 20 when necessary, employ an inert solvent such as those employed for the reduction of halocarbons of 1 to 6 carbons, preferably dichloromethane or 1,2-dichloroethane. A compound of Formula (XIII) is then converted to a compound of Formula (XVI) [Formula (I) 25 where X = CHOH] by reaction with a metalloc derivative of a compound of Formula (XV). Such a metalloc derivative is prepared by treatment with a base (X = H) or other metallating agents (X = halogen). Metallating agents, and the inert solvents for such metallations, include 30 those defined for the first step of Scheme III. A compound of Formula (XVI) [Formula (I) where X = CHOH] is oxidized to a compound of Formula (XVII) (Formula (I) where X = CO) using an oxidizing agent and inert solvent, both of which are defined the same as for the 35 second step of Scheme IV.

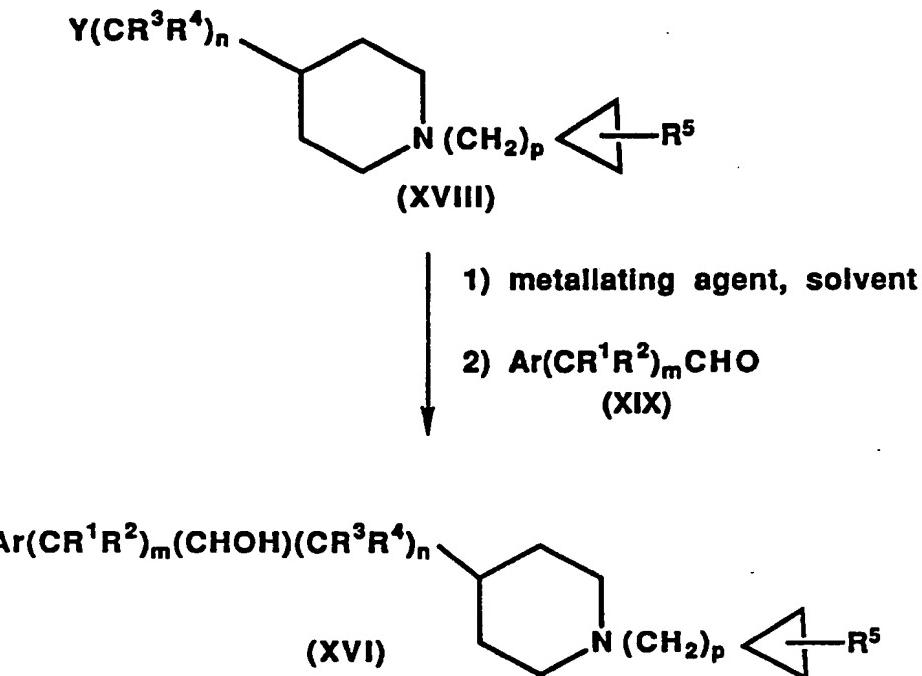
16

SCHEME IV

5 Alternatively, some of the compounds of this
 invention may be prepared using the procedures shown in
 Scheme V. A compound of Formula (XVIII) is converted to
 its metallo derivative with either a base (if Y = H,
 halogen) or other metallating agents (if Y = halogen) in
 10 an inert solvent. The choices of metallating agent and
 inert solvent are defined as for the first step of

17

Scheme III. Such a metallo derivative is reacted with an aldehyde of Formula (XIX) in the same inert solvent to afford a compound of Formula (XVI) [Formula (I) where X = CHO]. Reaction temperatures range from about -100°
 5 to 200°C, preferably about -78° to 80°C.

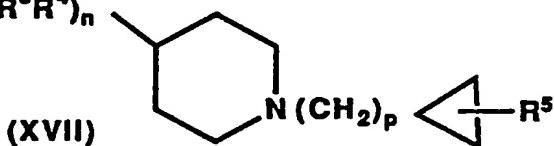
SCHEME V

10

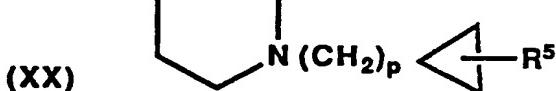
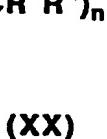
Some of the compounds of this invention may be prepared according to Scheme VI. A compound of Formula (XVII) [Formula (I) where X = CO] is reacted with an amine of Formula $\text{HNR}^{10}\text{R}^{11}$ in the presence of a reducing agent in an inert solvent to give a compound of Formula (XX) [Formula (I) where X = $\text{CHNR}^{10}\text{R}^{11}$]. The choices of reducing agent and inert solvent are defined the same as for these in the last step of Scheme III. R^{10} and R^{11} independently may be H or alkyl of 1 to 6 carbons or
 15

18

taken together are an alkylene chain of 2 to 6 carbons. When R¹⁰ and R¹¹ are both H, an ammonium salt is used (preferably ammonium acetate) according to the prior art (see pp. 45-100 of House, Modern Synthetic Reaction, 5 cited supra).

SCHEME VI

HNR¹⁰R¹¹, reducing agent,
solvent

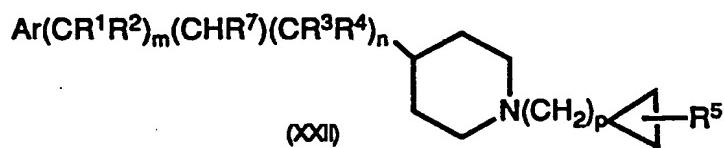
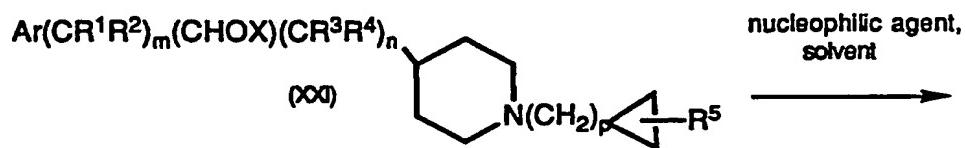
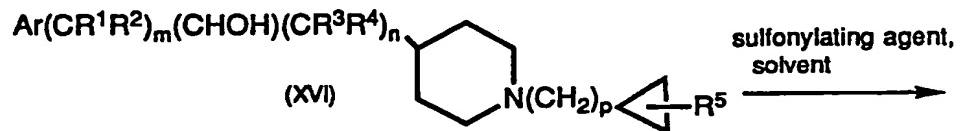


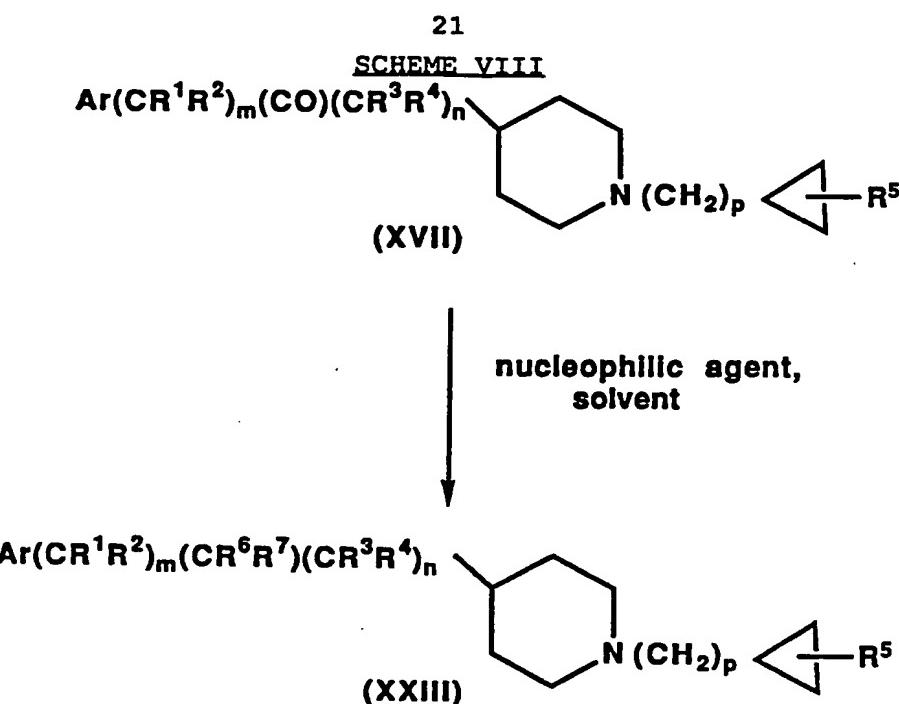
10 According to Scheme VII, a compound of Formula (XVI) [Formula I where X=CHOH] is treated with a sulfonylating agent, preferably methanesulfonyl chloride, p-toluenesulfonyl chloride or trifluoromethanesulfonic anhydride, in the presence of a 15 base, such as a trialkylamine, preferably triethylamine, an alkali metal hydride, preferably sodium hydride, an aromatic amine, preferably pyridine, or an alkali metal carbonate or alkoxide. Such a sulfonylation is performed in an inert solvent such as a halocarbon of 1 20 to 6 carbons, preferably dichloromethane, ethereal solvents, such as diethylether or tetrahydrofuran,

aromatic or non-aromatic hydrocarbons of 6 to 10 carbons, or alkanenitriles, preferably acetonitrile. A compound of Formula (XXI) [preferably where X is O₂SCH₃, O₂SC₆H₄-CH₃-p or O₂SCF₃] is formed from such a 5 sulfonylation and then is reacted with a nucleophilic reagent in an inert solvent to afford a compound of Formula (XXII) [Formula (I) where X is CHR⁷]. Such nucleophilic reagents include alkali metal alkoxides, alkali metal aluminum hydrides, dialkyl aluminum 10 hydrides, dialkylboranes, alkyl alkaline earth halides, preferably alkyl magnesium halides, dialkyl lithium cuprates, amines of the formula HNR¹⁰R¹¹, wherein R¹⁰ and R¹¹ are as defined above, alkali metal cyanides or alkali metal alkylsulfides. Inert solvents include 15 lower alkyl alcohols, alkanenitrile, preferably acetonitrile, ethereal solvents, such as diethyl ether and tetrahydrofuran, aromatic or non-aromatic hydrocarbons of 6 to 10 carbon atoms.

According to Scheme VIII, a compound of Formula 20 (XVII) [Formula (I) where X = CO] is reacted with a nucleophilic reagent in an inert solvent to give a compound of Formula (XXIII) [Formula (I) where X = CR⁶R⁷ where R⁶ and R⁷ are as defined in Formula (I)]. The choice of solvent is defined the same as for those in 25 Scheme VII. The nucleophilic reagents include alkali metal hydrides, dialkyl aluminum hydrides, trialkyl aluminum compounds, aryl or alkyl alkaline earth halides (preferably aryl or alkyl magnesium halides), aryl or alkyl lithiums or dialkyllithium cuprates.

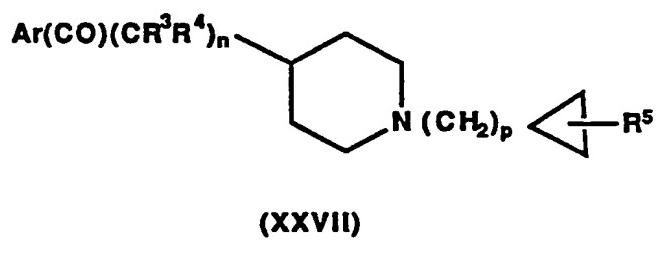
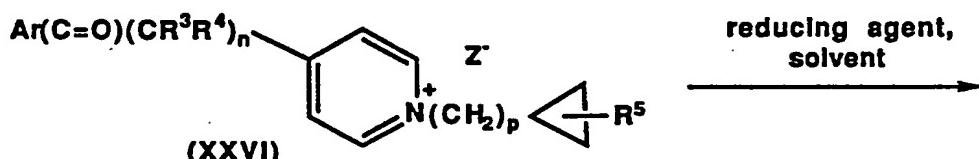
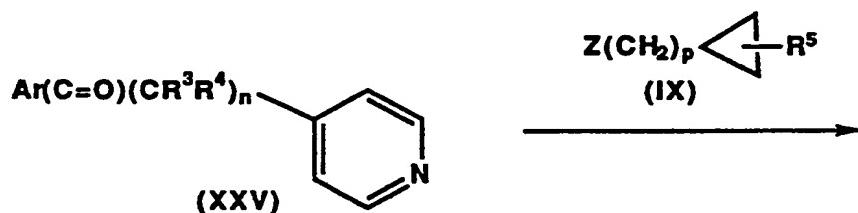
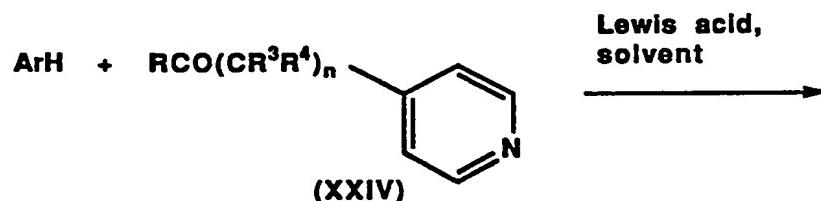
20

SCHEME VII



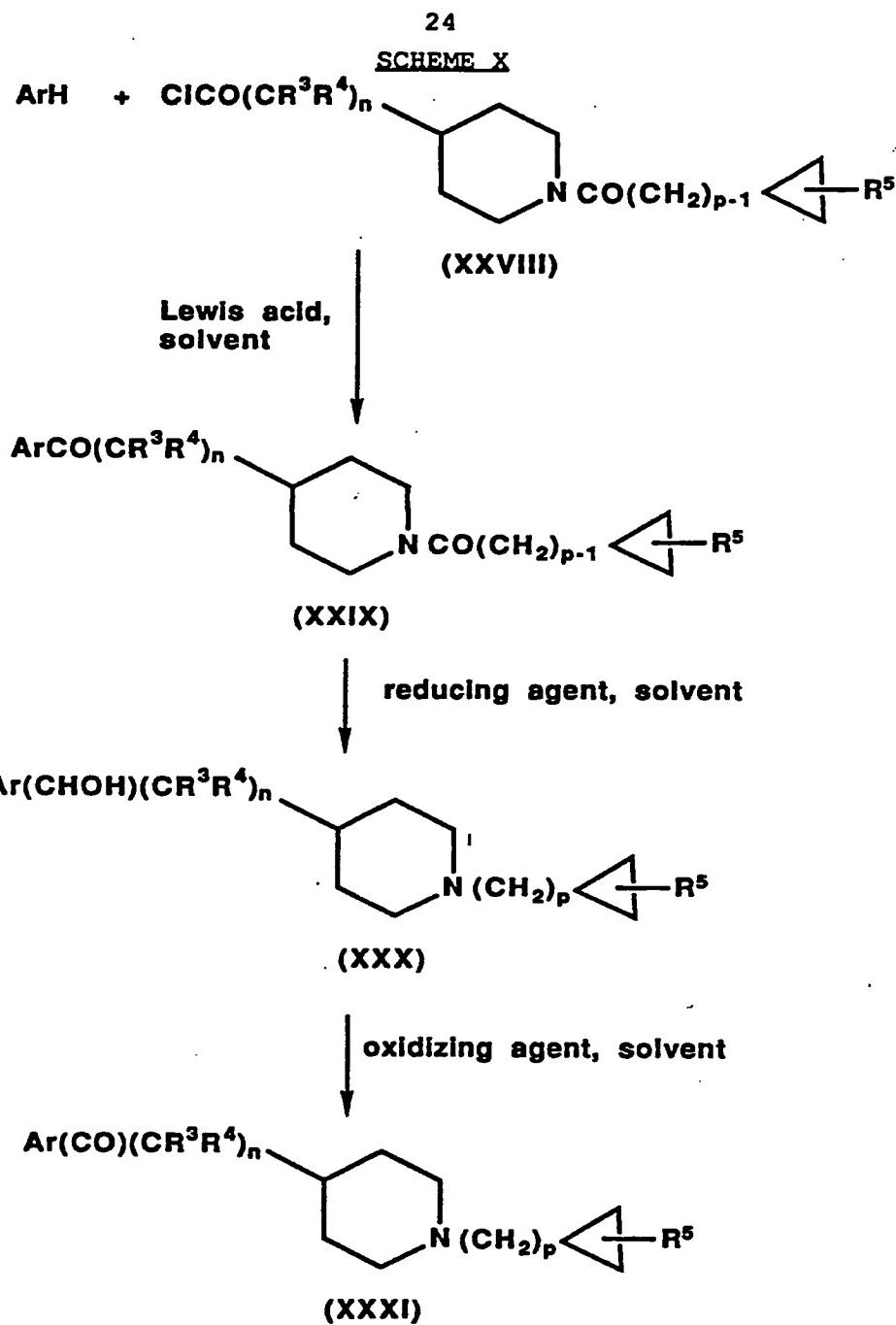
According to Scheme IX an acid derivative of Formula (XXIV) [R is halogen, OH or lower alkoxy and Ar and R³ and R⁴ are as defined in Formula (I)] is reacted with an aromatic compound in the presence of a Lewis acid in an inert solvent to afford a compound of Formula (XXV). Lewis acids include aluminum halides, alkylsulfonic acids, preferably methanesulfonic acid, polyphosphoric acid, or acetic acid. Inert solvents include carbon disulfide or aromatic hydrocarbons of 6 to 10 carbons bearing electron-withdrawing substituents, such as nitrobenzene. Compounds of Formula (XXV) are then converted to pyridinium salts (XXVI) with alkylating agents (IX). These compounds of Formula (XXVI) are then treated with reducing agents in an inert solvent to afford compounds of Formula (XXVII) [Formula (I), wherein m is 0 and X is CO]. The choices of alkylating agent (IX), reducing agent, inert solvents and reaction temperatures are the same as those defined in Scheme III.

22

SCHEME IX

- 5 Alternatively, according to Scheme X, a compound of
 Formula (XXVIII) is reacted with an aromatic compound in
 the presence of a Lewis acid and an inert solvent to
 provide a compound of Formula (XXIX). The choices of
 Lewis acid and inert solvents are defined the same as
 10 those in Scheme IX. Reaction temperatures range from

about 0° to 150°C. Compounds of Formula (XXIX) may be treated with reducing agents in inert solvents to give compounds of Formula (XXX) [Formula (I) wherein m is O and X is CHO]. The choices of reducing agent, solvent and reaction temperature are defined the same as those for the second step of Scheme I. Compounds of Formula (XXX) may be oxidized to compounds of Formula (XXXI) [Formula (I) wherein m is O and X = CO]. The choices of oxidizing agents, solvents and reaction temperatures are defined the same as those for the oxidation of compounds of Formula (XIV) to compounds of Formula (XIII) in Scheme (IV).

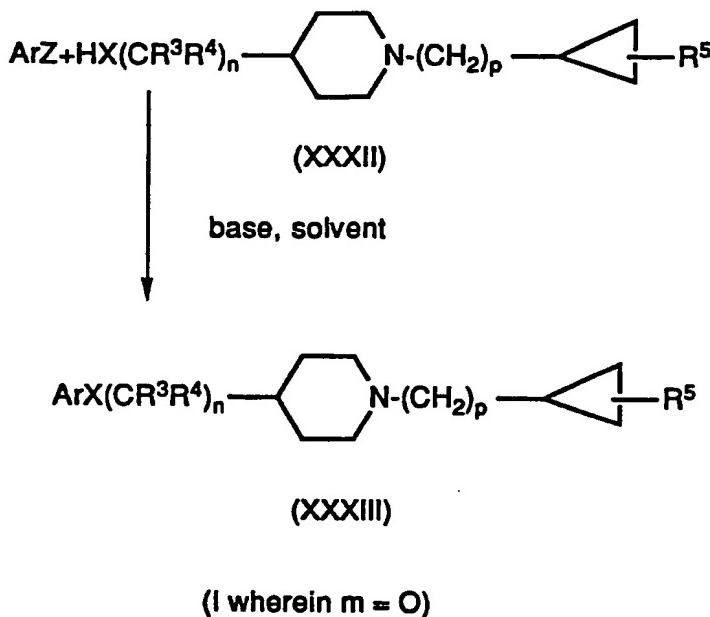


Compounds of Formula (I) may also be made according
 5 to Scheme XI. A compound of formula ArZ is reacted with

25

a compound of Formula (XXXII) (X is O, S or NR⁶) in the presence of a base and an inert solvent to yield a compound of Formula (XXXIII) [Formula (I) wherein m is O]. Ar is preferably a phenyl ring substituted with an electron withdrawing group or a heteroaryl ring. Z is halogen, preferably fluorine or chlorine. The choices for base and solvent are as defined in the first step of Scheme I.

10

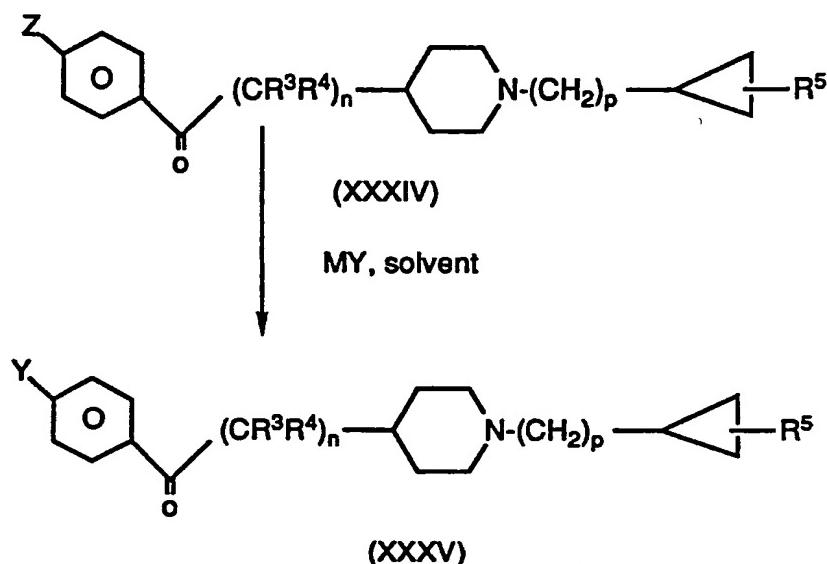
SCHEME XI

Compounds of Formula (I) may also be prepared according to Scheme XII. A compound of Formula (XXXIV) [wherein Z is halogen, preferably fluorine] is reacted with a compound MY [M is an alkali metal or an alkaline earth metal and Y is a nucleophile selected from the group: azide, alkoxide of 1 to 6 carbon atoms, alkylthioxide of 1 to 6 carbon atoms, cyanide, halide, NH₂, alkylamide of 1 to 6 carbon atoms or dialkylamide

26

of 2 to 6 carbon atoms] in an inert solvent at a reaction temperature of about 25-200°C and preferably 100-150°C, to yield a compound of Formula XXXV [Formula I, wherein m is 0 and X is C=O]. The inert solvent may 5 be the same as those defined in the first step of Scheme I. Compounds of formula MY may be generated *in situ* from a compound of formula HY and a base chosen from the bases defined for the first step of Scheme I.

10

SCHEME XII

Experimental Section

Analytical data were recorded for the compounds described below using the following general procedures.

Infrared spectra were recorded on a Perkin-Elmer Model

- 5 1600 FT-IR spectrometer; absorbances are recorded in cm^{-1} and intensities are denoted s (strong), m (moderate) and w (weak). Proton NMR spectra were recorded on a IBM-Bruker FT-NMR spectrometer (200 MHz or 300 MHz); chemical shifts were recorded in ppm (δ) from
10 an internal tetramethylsilane standard in deuteriochloroform or deuteriodimethylsulfoxide and coupling constants (J) are reported in Hz. Mass spectra (MS) or high resolution mass spectra (HRMS) were recorded on Finnegan MAT 8230 spectrometer or Hewlett
15 Packard 5988A model spectrometer. Melting points were recorded on a Buchi Model 510 melting point apparatus and are uncorrected. Boiling points are uncorrected.

Reagents were purchased from commercial sources and, where necessary, purified prior to use according to
20 the general procedures outlined by D. D. Perrin and W. L. F. Armarego, Purification of Laboratory Chemicals, 3rd ed., (New York:Pergamon Press, 1988).

Chromatography was performed on silica gel using the solvent systems indicated below. For mixed solvent
25 systems, the volume ratios are given. Parts and percentages are by weight unless otherwise specified.

Intermediate compounds of Formula (IV) (where X=O) are exemplified in the following Tables 1-5, these intermediate compounds are then further reduced by
30 various processes to yield some of the active antipsychotic compounds of Formula (I) (Tables 6-10). Compounds of Formula (I) are further exemplified in Tables 11-17.

Example 1Synthesis of 1-(Cyclopropylmethyl)-4-(4'-fluorophenoxyethyl)piperidineA. 1-(Cyclopropylcarbonyl)-4-hydroxymethylpiperidine

5 A solution of 1-(cyclopropylcarbonyl)-4-carboethoxy piperidine (35 g, 156 mmol) in anhydrous tetrahydrofuran (350 mL) was stirred at ambient temperature under a nitrogen atmosphere. A solution of lithium borohydride in tetrahydrofuran (2 M, 78 mL, 156 mmol) was added
10 dropwise. Trimethyl borate (1.77 mL, 15.7 mmol) was added, then the reduction mixture was stirred for about 48 hours. Water was added dropwise with vigorous stirring until the vigorous gas evolution ceased. The mixture was diluted twofold with water and extracted
15 three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. Vacuum distillation (bp 165°C, 0.5 mm Hg) gave a clear, colorless liquid (18.2 g): IR (neat): 3410 (br s), 3094 (w), 3008 (s), 2918 (s), 2858 (s), 1738 (m), 1613 (s), 1448 (s), 1375 (s), 1316 (s);
20 $^1\text{H-NMR}$: 4.7-4.5 (m, 1H), 4.4-4.1 (m, 1H), 3.6-3.4 (m, 2H), 3.2-2.5 (m, 3H), 2.0-1.7 (m, 4H), 1.4-1.1 (m, 1H), 1.0-0.8 (m, 2H), 0.8-0.65 (m, 2H); HRMS:Calcd for C₁₀H₁₇NO₂:183.1259; Found: 183.1250; Anal.:Calcd for
25 C₁₀H₁₇NO₂: C, 65.54, H, 9.35, N, 7.64; Found: C, 65.83, H, 9.43, N, 7.50.

B. 1-(Cyclopropylcarbonyl)-4-(methanesulfonyloxy)piperidine

30 A solution of 1-(cyclopropylcarbonyl)-4-hydroxymethyl-piperidine from Step A (6.0 g, 33 mmol) and triethylamine (11.9 g, 16.4 mL, 118 mmol) in dichloromethane (150 mL) was stirred at about 0°C under a nitrogen atmosphere. A solution of methanesulfonyl
35 chloride (4.5 g, 3.0 mL, 39 mmol) in dichloromethane (20

mL) was added dropwise. The reaction mixture was then stirred at about 0-5°C for 35 minutes. The pale yellow turbid mixture was poured into a separatory funnel, washed once with a 1 N hydrochloric acid solution (ice-cold, 100 mL), twice with a saturated sodium bicarbonate solution (100 mL) and once with brine (100 mL). The organic solution was dried over magnesium sulfate, filtered and concentrated in vacuo to give a pale yellow oil (8.5 g): ¹H-NMR: 4.8-4.5 (m, 1H), 4.4-4.2 (m, 1H), 4.2-3.95 (m, 2H), 3.2-2.8 (m, 4H), 2.7-2.5 (m, 1H), 2.2-1.6 (m, 4H), 1.5-1.1 (m, 2H), 1.05-0.9 (m, 2H), 0.85-0.7 (m, 2H); MS:261.

15 C. 1-(Cyclopropylcarbonyl)-4-(4'-fluorophenoxyethyl)piperidine

Sodium hydride (50% in oil, 1.0 g, 20 mmol) was washed with hexanes twice, then suspended in anhydrous tetrahydrofuran (20 mL) with stirring under a nitrogen atmosphere. A solution of 4-fluorophenol (2.13 g, 19 mmol) in tetrahydrofuran (10 mL) was added dropwise with vigorous gas evolution. The reaction mixture was stirred at room temperature for 15 minutes, then a solution of 1-cyclopropylcarbonyl-4-methane-sulfonyloxy piperidine (983 mg, 3.77 mmol) from Step B, in tetrahydrofuran (10 mL) was added dropwise. The reaction mixture was then stirred at reflux temperature for about 22 hours, cooled to ambient temperature, poured onto a 2 N sodium hydroxide solution and mixed. The aqueous mixture was extracted three times with ether; the combined organic layers were washed with a 2 N sodium hydroxide solution, dried over magnesium sulfate and filtered. Solvent was removed in vacuo to give a yellow liquid.

35 Column chromatography (ethyl acetate) gave, after removal of solvent in vacuo, the product, a clear,

30

colorless liquid (617 mg): $^1\text{H-NMR}$: 7.05-6.75 (m, 4H), 4.8-4.55 (br m, 1H), 4.45-4.2 (m, 1H), 3.9-3.6 (br s, 2H), 3.25-3.0 (br t, 1H, J=6), 2.8-2.5 (br t, 1H, J=6), 2.2-1.7 (m, 4H), 1.5-1.2 (m, 2H), 1.05-0.9 (m, 2H), 0.8-5 0.7 (m, 2H); HRMS:Calcd for $\text{C}_{16}\text{H}_{20}\text{FNO}_2$:277.1478; Found: 277.1466; Anal.:Calcd for $\text{C}_{16}\text{H}_{20}\text{FNO}_2$:C, 69.29, H, 7.27, N, 5.05, F, 6.85; Found: C, 69.14, H, 7.41, N, 5.04, F, 7.04.

10 D. 1-(Cyclopropylmethyl)-4-
(4¹-fluorophenoxyethyl)-piperidine

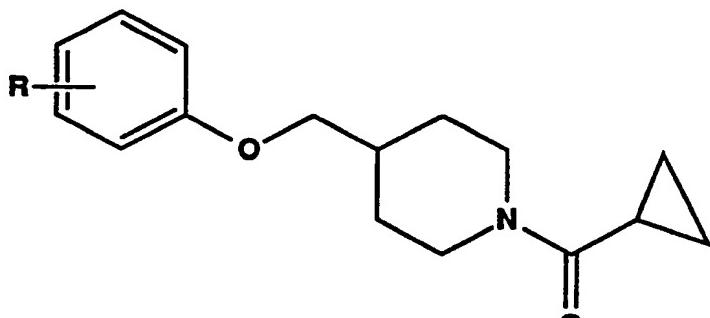
A solution of 1-(cyclopropylcarbonyl)-4-(4¹-fluorophenoxyethyl)piperidine (316 mg, 1.14 mmol) in anhydrous tetrahydrofuran (5 mL) was stirred at ambient 15 temperature under a nitrogen atmosphere. A solution of lithium aluminum hydride in tetrahydrofuran (1 M, 10 mL, 10 mmol) was added dropwise via syringe. The reaction mixture was then stirred at reflux temperature for 24 hours, then it was cooled to room temperature. Ethyl 20 acetate (10 mL) was added dropwise, then water (0.5 mL), a 2 N sodium hydroxide solution (0.5 mL), water (1.5 mL) were added sequentially. The resulting suspension was filtered through Celite® the inorganic salts were washed with copious amounts of ethyl acetate. The filtrate was 25 dried over magnesium sulfate and filtered. Solvent was removed in vacuo to give the product, a pale yellow white solid (266 mg, 89% yield): $^1\text{H-NMR}$: 7.0-6.7 (m, 4H), 3.7 (d, 3H, J=7), 3.05 (br d, 2H, J=10), 2.2 (d, 2H, J=7), 2.0-1.6 (m, 4H), 1.5-1.25 (m, 2H), 0.95-0.75 (m, 30 1H), 0.65-0.5 (m, 2H), 0.1-0.0 (m, 2H); MS:263; Anal.: Calcd. for $\text{C}_{16}\text{H}_{22}\text{FNO} \cdot 0.5\text{H}_2\text{O}$: C, 70.50, H, 8.23, N, 5.52; Found: C, 70.49, H, 8.44, N, 5.14.

31

The compounds of Table 1 may be prepared by the method described in Example 1C using the appropriate hydroxy aromatic compound and the appropriate polar solvent.

5

Table 1



(II)

10

	<u>Ex.</u>	<u>R</u>	<u>mp (°C)</u>
	1C	4-F	(a)
	2	4-Cl	82-83 (b)
	3	4-CH ₃ O	54-56 (c)
15	4	H	
	5	4-Br	
	6	4-I	
	7	4-NO ₂	
	8	4-(CH ₃) ₂ N	
20	9	4-NHCOCH ₃	
	10	4-CH ₃	
	11	4-t-C ₄ H ₉	105-109 (d)
	12	4-C ₂ H ₅ O	
	13	4-NHCHO	
25	14	4-CO ₂ CH ₃	111-112 (e)
	15	4-COCH ₃	98-101 (f)
	16	4-SCH ₃	107-109 (g)
	17	4-SO ₂ N(CH ₃) ₂	

32

Table 1 (continued)

<u>Ex.</u>	<u>R</u>	<u>mp (°C)</u>
18	4-CF ₃	
19	4-CCl ₃	
5 20	4-CH ₂ CF ₃	
21	4-COCF ₃	
22	4-CH ₂ CH ₂ F	
23	4-SCOCH ₃	
24	4-CN	
10 25	4-CON(CH ₃) ₂	
26	4-N ₃	
27	4-CH=CH ₂	
28	4-C ₆ H ₅	(h)
29	3-Cl	
15 30	3-Br	
31	3-I	
32	3-F	
33	3-CH ₃ O	
34	3-C ₂ H ₅ O	
20 35	3-CH ₃	
36	3-C ₂ H ₅	
37	3-CO ₂ CH ₃	
38	3-COCH ₃	
39	3-CF ₃	
25 40	3-CCl ₃	
41	3-CH ₂ CF ₃	
42	3-COCF ₃	
43	3-CH ₂ CH ₂ F	
44	3-CN	
30 45	3-CON(CH ₃) ₂	
46	3-CHO	
47	3-N ₃	
48	3-NHCHO	
49	3-NHCOCH ₃	
35 50	3-NO ₂	

33

Table 1 (continued)

<u>Ex.</u>	<u>R</u>	<u>mp (°C)</u>
51	3-(CH ₃) ₂ N	(i)
52	3-SCH ₃	
5	3-SO ₂ N(CH ₃) ₂	
53	3-SCOCH ₃	
54	2-F	
55	2-Br	
56	2-Cl	
57	2-I	
10	2-CH ₃ O	
58	2-CH ₃	
59	2-CO ₂ CH ₃	
60	2-COCH ₃	
61	2-CF ₃	
62	2-CCl ₃	
15	2-CH ₂ CF ₃	
63	2-COCF ₃	
64	2-CH ₂ CH ₂ F	
65	2-CN	
66	2-CON(CH ₃) ₂	
67	2-CHO	
20	2-N ₃	
68	2-NHCHO	
69	2-NHCOCH ₃	
70	2-NO ₂	
71	2-SCH ₃	
72	3,4-F ₂	(j)
25	3,4-Cl ₂	(k)
73	3,4-(CH ₃ O) ₂	
74	2,6-Br ₂ -4-CH ₃	
75	2,6-Br ₂ -4-NO ₂	
76	2,4-Cl ₂ -6-NO ₂	
77	2,4-Cl ₂	
30	3,5-Cl ₂	
78		
79		
80		
81		
82		
35		
83		

34

Table 1 (continued)

<u>Ex.</u>	<u>R</u>	<u>mp (°C)</u>
84	3-(C ₂ H ₅) ₂ N	
85	2,4-F ₂	
5 86	2,3-F ₃	
87	2,3-(CH ₃ O) ₂	
88	3,4-(CH ₃) ₂	
89	2,4-(CH ₃) ₂	
90	2,4-(NO ₂) ₂	
10 91	3-(OC ₂ H ₅)4-OCH ₃	
92	4-(OCH ₃)-3(OC ₂ H ₅)	
93	5-F-2-NO ₂	
94	2-(CH ₃ O)-4-(NO ₂)	
95	3-(CH ₃ O)-4-(NO ₂)	
15 96	3,4-OCH ₂ O	
97	3-CH ₃ -4-NO ₂	
98	4-CH ₃ -3-NO ₂	
99	2-CH ₃ -3-NO ₂	
100	2-NO ₂ -3-CH ₃	
20 101	F ₅	(1)
102	Br ₅	
103	Cl ₅	
104	2,3,5,6-F ₄	
105	2,3,5,6-Cl ₄	
25 106	2,3,5,6-Br ₄	
107	2,4,5-F ₃	
108	2,4,5-Cl ₃	
109	2,4,5-Br ₃	
110	3,4,5-(CH ₃ O) ₃	108-110 (m)
30 111	4-C ₆ H ₅ O	109-110 (n)
112	4-F-C ₆ H ₄	133-135 (o)
113	4-CH ₃ O-C ₆ H ₄	143-145 (p)

Footnotes for Table 1

- (a) Anal.: Calcd for $C_{16}H_{20}FNO_2$: C, 69.29, H, 7.27, N, 5.05, F, 6.85; Found: C, 69.14, H, 7.41, N, 5.04, F, 7.04.
- 5 (b) Anal.: Calcd for $C_{16}H_{20}ClNO_2$: C, 65.41, H, 6.86, N, 4.77, Cl, 12.07; Found: C, 65.18, H, 6.77, N, 4.67, Cl, 12.14.
- (c) Anal.: Calcd for $C_{17}H_{23}NO_3$: C, 70.56, H, 8.01, N, 4.84; Found: C, 70.59, H, 8.02, N, 4.94.
- 10 (d) 1H -NMR ($CDCl_3$): 7.4-7.2 (m, 2H), 6.9-6.7 (m, 2H), 4.8-4.6 (m, 1H), 3.9-3.7 (m, 2H), 3.2-3.0 (m, 1H), 2.7-2.5 (m, 1H), 2.1-1.7 (m, 3H), 1.5-1.3 (m, 7H), 1.3 (s, 9H); MS:315.
- (e) Anal.: Calcd for $C_{18}H_{23}NO_4$: C, 68.12, H, 7.30, N, 4.41; Found: C, 68.20, H, 7.48, N, 4.63.
- 15 (f) 1H -NMR ($CDCl_3$): 8.0 (d, 2H, $J=8$), 6.9 (d, 2H, $J=8$), 4.7 (m, 1H), 4.4 (m, 1H), 3.9 (m, 2H), 3.2 (m, 1H), 2.7 (m, 1H), 2.6 (s, 3H), 2.2-1.7 (m, 4H), 1.4 (m, 2H); MS:301.
- 20 (g) Anal.: Calcd for $C_{17}H_{23}NO_2S$: C, 66.85, H, 7.59, N, 4.58, S, 10.67; Found: C, 66.92, H, 7.74, N, 4.46, S, 10.23
- (h) 1H -NMR ($CDCl_3$): 7.6-7.2 (m, 7H), 7.0 (d, 2H, $J=7$), 4.8-4.6 (m, 1H), 4.4-4.2 (m, 1H), 3.9 (br s, 2H), 3.3-3.1 (m, 2H), 2.8-2.6 (m, 2H), 2.2-1.7 (m, 3H), 1.4-1.2 (m, 1H), 1.1-0.9 (m, 2H), 0.9-0.7 (m, 2H).
- 25 (i) 1H -NMR ($CDCl_3$): 7.15 (t, 1H, $J=8$), 6.15 (d, 1H, $J=9$), 6.1-6.0 (m, 2H), 4.7-4.55 (m, 1H), 4.35-4.2 (m, 1H), 3.9-3.7 (m, 2H), 3.2-3.0 (m, 1H), 2.9 (s, 6H), 2.8-2.5 (m, 1H), 2.2-1.7 (m, 4H), 1.5-1.2 (m, 2H), 1.05-0.9 (m, 2H), 0.8-0.65 (m, 2H); HRMS: Calcd for $C_{18}H_{26}N_2O_2$: 302.1994; Found: 302.1994.
- (j) 1H -NMR ($CDCl_3$, 300 MHz): 7.05 (q, 1H, $J=8$), 6.75-6.65 (m, 1H), 6.65-6.5 (m, 1H), 4.75-4.6 (m, 1H), 4.4-4.2 (m, 1H), 3.85-3.7 (m, 2H), 3.15 (br t, 1H,
- 30
35

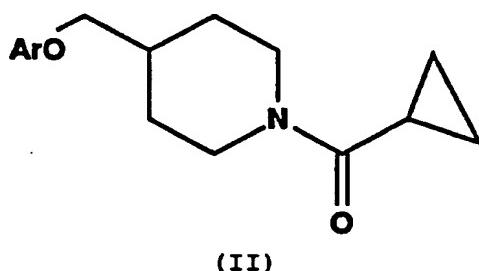
Footnotes for Table 1 (continued)

- J=7), 2.65 (br t, 1H, J=7), 2.15-1.7 (m, 4H), 1.5-1.2 (m, 2H), 1.1-0.9 (m, 2H), 0.9-0.75 (m, 2H); HRMS: Calcd for C₁₆H₁₉F₂NO₂: 295.1384; Found:
- 5 295.1385
- (k) ¹H-NMR (CDCl₃): 7.4-7.2 (m, 1H), 7.05-6.95 (m, 1H), 6.8-6.65 (m, 1H), 4.8-4.55 (m, 1H), 4.4-4.2 (m, 1H), 3.9-3.7 (m, 2H), 3.3-3.0 (m, 1H), 2.8-2.5 (m, 1H), 2.2-1.7 (m, 4H), 1.5-1.2 (m, 2H), 1.06-0.9 (m, 2H), 10 0.85-0.7 (m, 2H); HRMS: Calcd for C₁₆H₁₉Cl₂NO₂: 327.0793; Found: 327.0788.
- (l) ¹H-NMR (CDCl₃): 4.75-4.55 (m, 1H), 4.4-4.2 (m, 1H), 4.1-3.9 (m, 2H), 3.25-3.05 (m, 1H), 2.75-2.5 (m, 1H), 2.2-1.7 (m, 3H), 1.5-1.2 (m, 2H), 1.05-0.9 (m, 2H), 15 0.85-0.6 (m, 2H); Calcd for C₁₆H₁₆F₅NO₂: 329.1101; Found: 349.1100.
- (m) Anal.: Calcd for C₁₉H₂₇NO₅: C, 65.31, H, 7.79, N, 4.01; Found: C, 65.41, H, 7.76, N, 4.26.
- (n) Anal.: Calcd for C₂₂H₂₅NO₂: C, 75.19, H, 7.17, N, 3.99; Found: C, 75.15, H, 7.12, N, 3.91.
- 20 (o) ¹H-NMR (DMSO, 300 MHz): 7.65 (dd, 2H, J=8, 6), 7.55 (d, 2H, J=8), 7.3 (t, 2H, J=8), 7.05 (d, 2H, J=8), 4.5-4.3 (m, 2H), 3.9 (d, 2H, J=7), 3.2-3.0 (m, 1H), 2.7-2.55 (m, 1H), 2.1-1.7 (m, 4H), 1.4-1.05 (m, 2H), 25 0.85-0.6 (m, 4H); MS:354.
- (p) ¹H-NMR (DMSO, 300 MHz): 7.55 (2 x d, 4H, J=8), 7.0 (d, 4H, J=8), 4.5-4.3 (m, 2H), 3.9 (d, 2H, J=7), 3.8 (s, 3H), 3.2-3.1 (m, 1H), 2.7-2.6 (m, 1H), 2.1-1.75 (m, 4H), 1.35-1.1 (m, 2H), 0.8-0.6 (m, 4H); HRMS: 30 Calcd for C₂₃H₂₇NO₃: 365.1991; Found: 365.2001.

37

The compounds of Table 2 may be prepared by the method described in Example 1C using the appropriate hydroxy aromatic compound and the appropriate polar solvent.

5

Table 2

10	<u>Ex.</u>	<u>Ar</u>	<u>mp (°C)</u>
	114	2-naphthyl	150-152 (a)
	115	1-naphthyl	
	116	2,4-dichloro-1-naphthyl	
	117	4-indolyl	
15	118	5-indolyl	
	119	5-isoquinolinyl	
	120	4-pyridyl	(b)
	121	3-pyridyl	
	122	2-methyl-4-quinolinyl	
20	123	3-nitro-2-pyridyl	
	124	4-quinolinyl	(c)
	125	5-quinolinyl	
	126	5-pyrimidyl	

25 Footnotes for Table 2

(a) Anal.: Calcd for C₂₀H₂₃NO₂•0.2H₂O: C, 76.75, H, 7.53, N, 4.47; Found: C, 76.91, 76.89, H, 7.60, 7.53, N, 4.56, 4.32.

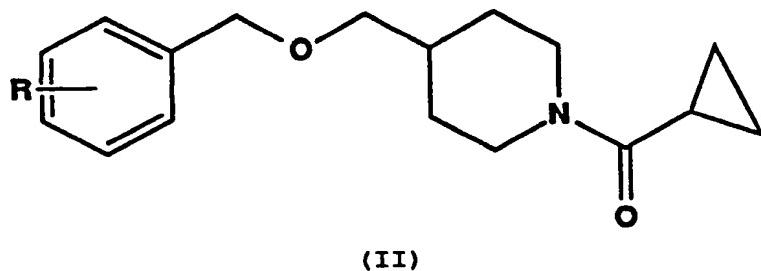
Footnotes for Table 2 (continued)

- (b) $^1\text{H-NMR}$ (CDCl_3): 8.45 (d, 2H, $J=6$), 6.8 (d, 2H, $J=6$),
4.7 (br d, 1H, $J=10$), 4.3 (br d, 1H, $J=10$), 3.95-3.8
(m, 2H), 3.15 (br t, 1H, $J=10$), 2.65 (br t, 1H,
5 $J=10$), 2.2-1.75 (m, 4H), 1.5-1.25 (m, 2H), 1.05-0.95
(m, 2H), 0.8-0.65 (m, 2H); HRMS: Calcd for
 $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_2$: 260.1525; Found: 260.1537.
- (c) $^1\text{H-NMR}$ (CDCl_3): 8.7 (d, 1H, $J=6$), 8.2 (d, 1H, $J=8$),
8.05 (d, 1H, $J=8$), 7.7 (td, 1H, $J=6,1$), 7.5 (t, 1H,
10 $J=6$), 6.7 (d, 1H, $J=6$), 4.75 (br d, 1H, $J=10$), 4.35
(br d, 1H, $J=10$), 4.15-4.0 (m, 2H), 3.2 (br t, 1H,
 $J=10$, 2.7 (br t, 1H, $J=10$); HRMS: Calcd for
 $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_2$: 310.1681; Found: 310.1690.

39

The compounds of Table 3 may be prepared according to the procedure described for Example 1C using the appropriate hydroxymethyl aromatic compound and polar solvent.

5

Table 3

10	<u>Ex.</u>	<u>R</u>	<u>mp (°C)</u>
	127	4-F	
	128	4-Cl	
	129	4-Br	
	130	4-I	
15	131	H	
	132	4-CH ₃ O	
	133	4-C ₂ H ₅ O	
	134	4-TBDMSO	(a)
	135	4-NO ₂	
20	136	4-(CH ₃) ₂ N	
	137	4-NHCOCH ₃	
	138	4-N ₃	
	139	4-CH ₃	
	140	4-C ₂ H ₅	
25	141	4-CO ₂ CH ₃	
	142	4-COCH ₃	
	143	4-CF ₃	
	144	4-CHO	
	145	4-CN	

40

Table 3 (continued)

<u>Ex.</u>	<u>R</u>	<u>mp (°C)</u>
146	4-CON(CH ₃) ₂	
147	4-SCH ₃	
5 148	3-F	
149	3-Cl	
150	3-Br	
151	3-I	
152	3-CH ₃ O	
10 153	3-C ₂ H ₅ O	
154	3-CH ₃	
155	3-C ₂ H ₅	
156	3-CO ₂ CH ₃	
157	3-COCH ₃	
15 158	3-CF ₃	
159	3-CN	
160	3-CON(CH ₃) ₂	
161	3-CHO	
162	3-N ₃	
20 163	3-NO ₂	
164	3-NHCOCH ₃	
165	3-NHCHO	
166	3-(CH ₃) ₂ N	
167	3-SCH ₃	
25 168	3-SO ₂ N(CH ₃) ₂	
169	2-F	
170	2-Cl	
171	2-Br	
172	2-I	
30 173	2-CH ₃ O	
174	2-CH ₃	
175	2-CO ₂ CH ₃	

41

Table 3 (continued)

<u>Ex.</u>	<u>B</u>	<u>mp (°C)</u>
176	2-COCH ₃	
177	2-CF ₃	
5 178	2-CN	
179	2-N ₃	
180	2-NHCHO	
181	2-NHCOCH ₃	
182	2-NO ₂	
10 183	2-SCH ₃	
184	3,4-F ₂	
185	3,4-Cl ₂	
186	3,4-(CH ₃ O) ₂	
187	2,4-Cl ₂	
15 188	2,4-F ₂	
189	2,4-(CH ₃ O) ₂	
190	3,4-F ₂	
191	3,5-Cl ₂	
192	3,4-(CH ₃) ₂	
20 193	2,4-(NO ₂) ₂	
194	3,4-(NO ₂) ₂	
195	3-CH ₃ O-4-NO ₂	
196	4-CH ₃ O-3-NO ₂	
197	3,4-OCH ₂ O-	
25 198	F ₅	
199	Cl ₅	
200	3,4,5-(CH ₃ O) ₃	

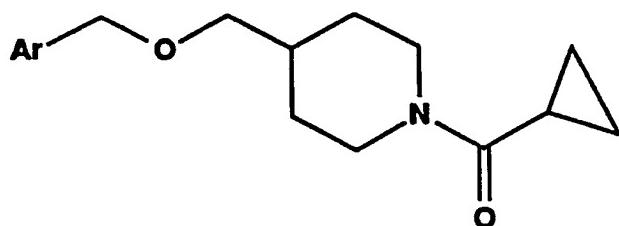
Footnote for Table 3

(a) TBDMS = t-butyldimethylsilyl.

42

The compounds of Table 4 may be prepared according to the method described in Example 1C using the appropriate hydroxy aromatic compound and the appropriate polar solvent.

5

Table 4

(II)

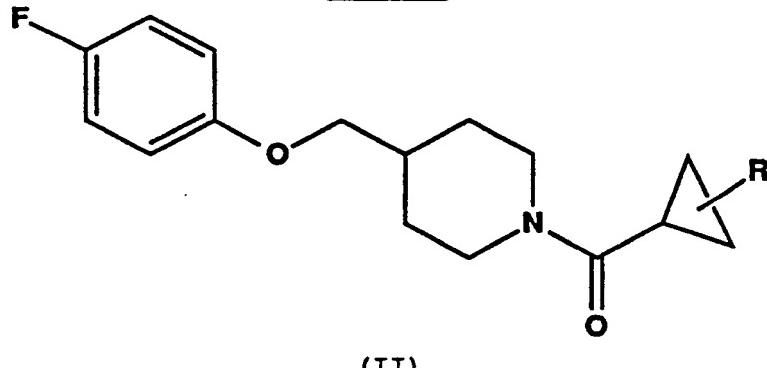
10

	<u>Ex.</u>	<u>Ar</u>	<u>mp (°C)</u>
	201	2-naphthyl	
	202	1-naphthyl	
	203	2-quinolinyl	
15	204	4-quinolinyl	
	205	2-pyridyl	
	206	3-pyridyl	
	207	4-pyridyl	
	208	2-pyrimidyl	
20	209	2-furyl	
	210	2-thienyl	

43

The compounds of Table 5 may be prepared according to the method of Example 1C using the appropriate 4-methanesulfonyloxypiperidine derivative.

5

Table 5

<u>Ex.</u>	<u>TR</u>	<u>Notes</u>
10	211	
	212	(a)
	213	(b)
	214	
	215	
15	216	
	2,2-Cl ₂	
	217	
	218	
	219	
	220	
20		

Footnotes for Table 5

(a) ¹H-NMR (CDCl₃, 300 MHz): 6.95 (t, 2H, J=7), 6.8 (dd, 2H, J=7, 6), 4.65 (br d, 1H, J=8), 4.25 (br d, 1H, J=8), 3.9-3.7 (m, 2H), 3.15 (br t, 1H, J=8), 2.65 (br t, 1H, J=8), 2.15-1.8 (m, 3H), 1.5-1.1 (m, 5H), 1.15 (d, 3H, J=7), 0.65-0.45 (m, 1H);

25

Footnotes for Table 5 (continued)

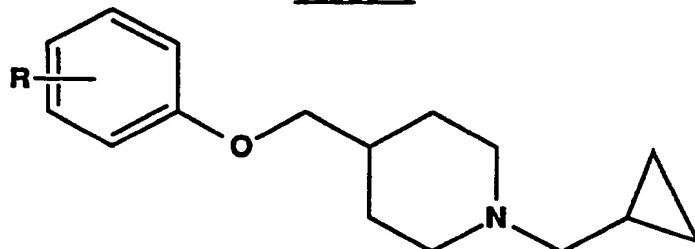
HRMS: Calcd for C₁₇H₂₂FNO₂: 291.1634; Found:
291.1636.

5 (b) ¹H-NMR (CDCl₃, 300 MHz): 7.05-6.9 (m, 2H), 6.9-6.8
(m, 2H), 4.65 (br t, 1H, J=10), 3.95 (br t, 1H,
J=10), 3.9-3.75 (m, 2H), 3.35-3.2 (m, 1H), 2.8-2.65
(m, 1H), 2.2-2.0 (m, 2H), 2.0-1.9 (m, 1H), 1.7-1.2
(m, 4H), 1.55 (d, 3H, J=7); HRMS: Calcd for
C₁₇H₂₀Cl₂FNO₂: 359.0855; Found: 359.0860.

Compounds of Formula (I) are exemplified in the following Tables 6-17.

The compounds of Tables 6, 7, 8, 9 and 10 may be prepared employing the procedure described for Example 5 1D with the appropriate 1-(cyclopropylcarbonyl)-piperidine derivative (Examples 2-220) and the appropriate reducing agent.

Table 6



	<u>Ex.</u>	<u>R</u>	<u>mp (°C)</u>
	1D	4-F	(a)
	221	4-Cl	(b)
15	222	4-CH ₃ O	37-39 (c)
	223	H	54-56 (d)
	224	4-Br	
	225	4-I	
	226	4-NH ₂	
20	227	4-(CH ₃) ₂ N	
	228	4-NHC ₂ H ₅	
	229	4-CH ₃	
	230	4-C ₆ H ₅	81-83 (e)
	231	4-C ₂ H ₅ O	
25	232	4-NHCH ₃	
	233	4-CH ₂ OH	120-121 (f)
	234	4-t-C ₄ H ₉	84-86 (g)
	235	4-SCH ₃	(h)
	236	4-SO ₂ N(CH ₃) ₂	
30	237	4-CF ₃	

46

Table 6 (continued)

<u>Ex.</u>	R	<u>mp (°C)</u>
238	4-CCl ₃	
239	4-CH ₂ CF ₃	
5 240	4-CH(OH)CH ₃	125-127 (i)
241	4-CH ₂ CH ₃ F	
242	4-SH	
243	4-CH ₂ NH ₂	(j)
244	4-CH ₂ N(CH ₃) ₂	
10 245	4-CH=CH ₂	
246	3-Cl	
247	3-Br	
248	3-I	
249	3-F	
15 250	3-CH ₃ O	
251	3-C ₂ H ₅ O	
252	3-CH ₃	
253	3-C ₂ H ₅	
254	3-CH ₂ OH	
20 255	3-CH(OH)CH ₃	
256	3-CF ₃	
257	3-CH ₂ CF ₃	
258	3-CH(OH)CF ₃	
259	3-CH ₂ CH ₂ F	
25 260	3-CH ₂ NH ₂	
261	3-CH ₂ N(CH ₃) ₂	
262	3-NHCH ₃	
263	3-NHC ₂ H ₅	
264	3-NH ₂	
30 265	3-N(CH ₃) ₂	
266	3-SCH ₃	
267	2-F	
268	2-Br	
269	2-Cl	
35 270	2-I	

47

Table 6 (continued)

<u>Ex.</u>	<u>R</u>	<u>mp (°C)</u>
271	2-CH ₃ O	
272	2-CH ₃	
5 273	2-CH ₂ OH	
274	2-CH(OH)CH ₃	
275	2-CF ₃	
276	2-CH ₂ CF ₃	
277	2-CH ₂ NH ₂	
10 278	2-CH ₂ N(CH ₃) ₂	
279	2-NHCH ₃	
280	2-NHC ₂ H ₅	
281	2-NH ₂	
282	2-SCH ₃	
15 283	3,4-F ₂	(k)
284	3,4-Cl ₂	
285	3,4-(CH ₃ O) ₂	
286	2,6-Br ₂ -4-CH ₃	
287	2,6-Br ₂ -4-NH ₂	
20 288	2,4-Cl ₂ -6-NH ₂	
289	2,4-Cl ₂	
290	3,5-Cl ₂	
291	3-(C ₂ H ₅) ₂ N	
292	2,4-F ₂	
25 293	2,3-F ₂	
294	2,3-(CH ₃ O) ₂	
295	3,4-(CH ₃) ₂	
296	2,4-(CH ₃) ₂	
297	2,4-(NH ₂) ₂	
30 298	3-(OC ₂ H ₅)-4-(OCH ₃)	
299	4-(OCH ₃)-3-(OC ₂ H ₅)	
300	5-F-2-NH ₂	
301	2-CH ₃ O-4-NH ₂	
302	3-CH ₃ O-4-NH ₂	
35 303	3-4-OCH ₂ O	

48

Table 6 (continued)

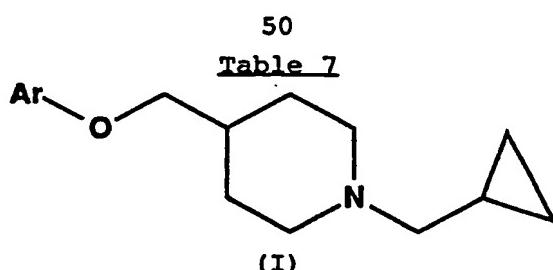
<u>Ex.</u>	<u>R</u>	<u>mp (°C)</u>
304	3-CH ₃ -4-NH ₂	
305	4-CH ₃ -3-NH ₂	
5 306	2-CH ₃ -3-NH ₂	
307	2-NH ₂ -3-CH ₃	
308	F ₅	(1)
309	Br ₅	
310	Cl ₅	
10 311	2,3,5,6-F ₄	
312	2,3,5,6-Cl ₄	
313	2,4,5-F ₃	
314	2,4,5-Cl ₃	
315	2,4,5-Br ₃	
15 316	3,4,5-(CH ₃ O) ₃	(m)

Footnotes for Table 6

- (a) ¹H-NMR: 7.0-7.0-6.7 (m, 4H), 3.7 (d, 3H, J=7), 3.05 (br d, 2H, J=10), 2.2 (d, 2H, J=7), 2.0-1.6 (m, 6H), 20 1.5-1.25 (m, 2H), 0.95-0.75 (m, 1H), 0.65-0.5 (m, 2H), 0.1-0.0 (m, 2H), MS: 263.
- (b) ¹H-NMR (200 MHz, CDCl₃-DMSO): 7.7 (d, 2H, J=8), 7.35 (d, 2H, J=8), 4.3-4.2 (m, 2H), 3.6-3.4 (m, 2H), 2.65 (d, 2H, J=6), 2.5-2.1 (m, 4H), 1.96-1.7 (m, 2H), 25 1.4-1.2 (m, 1H), 1.0-0.85 (m, 2H), 0.6-0.5 (m, 2H); HRMS: Calcd for C₁₆H₂₁ClNO: 279.1390; Found 279.1376.
- (c) ¹H-NMR (200 MHz, CDCl₃-DMSO): 7.15 (s, 4H), 4.25-4.1 (m, 2H), 4.2 (s, 3H), 3.6-3.4 (m, 2H), 2.65 (d, 2H, J=7), 2.55-2.1 (m, 5H), 1.95-1.75 (m, 2H), 1.4-1.25 (m, 1H), 1.0-0.85 (m, 2H), 0.6-0.45 (m, 2H).
- (d) Anal.: Calcd for C₁₆H₂₃NO: C, 78.26, H, 9.37, N, 5.71; Found: C, 77.94, H, 9.49, N, 5.55.
- (e) Anal.: Calcd for C₂₂H₂₇NO·0.125 H₂O: C, 81.67, H, 8.43, N, 4.33; Found: C, 81.86, 81.85, H, 8.64, 35 8.71, N, 4.13, 4.05.

Footnotes for Table 6 (continued)

- (f) Anal.: Calcd for $C_{17}H_{25}NO_2 \cdot 0.3 H_2O$: C, 72.72, H, 9.19, N, 4.99; Found: C, 72.98, 73.08, H, 9.04, 9.10, N, 4.97, 4.96.
- 5 (g) Anal.: Calcd for $C_{20}H_{31}NO$: C, 79.73, H, 10.30, N, 4.65; Found: C, 79.71, H, 10.18, N, 4.72.
- (h) 1H -NMR ($CDCl_3$, 300 MHz): 7.15 (d, 2H, J=8), 6.75 (d, 2H, J=8), 3.7 (d, 2H, J=7), 3.05 (br d, 2H, J=9), 2.25 (s, 3H), 2.15 (d, 2H, J=7), 2.0-1.6 (m, 5H), 1.45-1.3 (m, 2H), 0.9-0.7 (m, 1H), 0.5-0.35 (m, 2H), 0.1-0.0 (m, 2H); HRMS: Calcd for $C_{17}H_{25}NOS$: 291.1657; Found: 291.1653.
- (i) Anal.: Calcd for $C_{18}H_{27}NO_2$: C, 74.96, H, 9.09, N, 4.85; Found: C, 74.77, H, 9.38, N, 4.75.
- 15 (j) 1H -NMR ($CDCl_3$, 300 MHz): 7.15 (d, 2H, J=8), 6.8 (d, 2H, J=8), 3.75 (d, 2H, J=7), 2.9 (br d, 2H, J=10), 2.1 (d, 2H, J=7), 1.9-1.5 (m, 6H), 1.3-1.1 (m, 3H), 0.85-0.7 (m, 1H), 0.55-0.45 (m, 2H), 0.1-0.0 (m, 2H).
- 20 (k) 1H -NMR ($CDCl_3$, 300 MHz): 6.95 (q, 1H, J=8), 6.65-6.5 (m, 1H), 6.5-6.4 (m, 1H), 3.65 (d, 2H, J=7), 3.05 (br d, 2H, J=10), 2.2 (d, 2H, J=7), 2.0-1.8 (m, 2H), 1.8-1.6 (m, 3H), 1.5-1.3 (m, 2H), 0.9-0.7 (m, 1H), 0.65-0.5 (m, 2H), 0.10-0.0 (m, 2H); MS: 281.
- 25 (l) 1H -NMR ($CDCl_3$): 6.15 (s, 2H), 3.85 (s, 6H), 3.8 (s, 2H), 3.75 (d, 3H, J=7), 3.15 (br d, 2H, J=10), 2.3 (d, 2H, J=7), 2.1-1.7 (m, 5H), 1.65-1.4 (m, 2H), 1.0-0.8 (m, 1H), 0.6-0.45 (m, 2H), 0.15-0.05 (m, 2H), HRMS: Calcd for $C_{19}H_{29}NO_4$: 335.2096; Found: 335.2105.
- (m) 1H -NMR ($CDCl_3$, 200 MHz): 4.0 (d, 2H, J=7), 3.15 (br d, 2H, J=10), 2.3 (d, 2H, J=7), 2.05 (br t, 2H, J=7) 1.9-1.7 (m, 3H), 1.5-1.35 (m, 2H), 0.95-0.85 (m, 1H), 0.55-0.45 (m, 2H), 0.15-0.05 (m, 2H); HRMS: Calcd for $C_{16}H_{18}F_5NO$: 335.1308; Found: 335.1304.



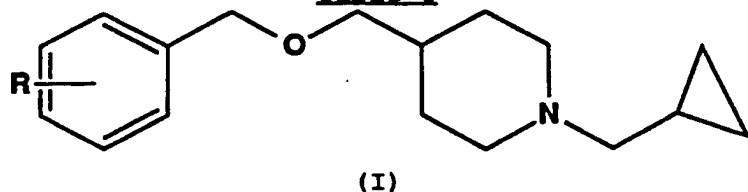
5	<u>Ex.</u>	<u>Ar</u>	<u>mp (°C)</u>
	317	2-naphthyl	69-71 (a)
	318	1-naphthyl	
	319	2-4-dichloro-1-naphthyl	
	320	4-indolyl	
10	321	5-indolyl	
	322	5-isoquinolinyl	
	323	4-pyridyl	53-54 (b)
	324	3-pyridyl	
	325	2-methyl-4-quinolinyl	
15	326	4-quinolinyl	85-86 (c)
	327	5-quinolinyl	
	328	5-pyrimidyl	

Footnotes for Table 7

- 20 (a) Anal.: Calcd for $C_{20}H_{25}NO \cdot 0.25H_2O$: C, 80.09, H, 8.58, N, 4.67; Found: C, 80.30, 80.40, H, 8.58, 8.65, N, 4.52, 4.70.
(b) Anal.: Calcd for $C_{15}H_{22}N_2O \cdot 0.25H_2O$: C, 71.82, H, 8.84, N, 11.17; Found: C, 71.84, 71.86, H, 9.07, 9.07, N, 10.98, 11.06.
(c) Anal.: Calcd for $C_{19}H_{24}N_2O \cdot 0.75H_2O$: C, 73.63, H, 8.29, N, 9.03; Found: C, 73.59, 73.86, H, 8.33, 8.33, N, 8.71, 8.77.

51

Table 8



<u>S</u>	<u>Ex.</u>	<u>R</u>	<u>mp (°C)</u>
	329	4-F	(a)
	330	4-Cl	
	331	4-Br	
	332	4-I	
10	333	H	
	334	4-CH ₃ O	
	335	4-C ₂ H ₅ O	
	336	4-TBDMSO	
	337	4-NH ₂	
15	338	4-(CH ₃) ₂ N	
	339	4-NHC ₂ H ₅	
	340	4-CH ₃	
	341	4-C ₂ H ₅	
	342	4-CH ₂ OH	
20	343	4-CH(OH)CH ₃	
	344	4-CF ₃	
	345	4-CH ₂	
	346	4-CH ₂ N(CH ₃) ₂	
	347	4-SCH ₃	
25	348	3-F	
	349	3-Cl	
	350	3-Br	
	351	3-I	
	352	3-CH ₃ O	
30	353	3-C ₂ H ₅ O	
	354	3-CH ₂ OH	
	355	3-CH(OH)CH ₃	
	356	3-CF ₃	

52

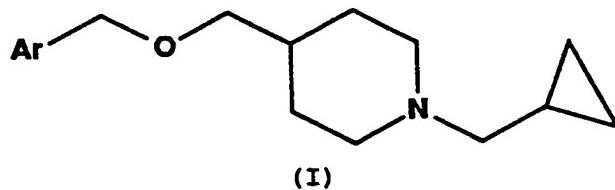
Table 8 (continued)

<u>Ex.</u>	R	<u>mp (°C)</u>
357	3-CH ₂ NH ₂	
358	3-CH ₂ N(CH ₃) ₂	
5 359	3-NH ₂	
360	3-NHC ₂ H ₅	
361	3-NHCH ₃	
362	3-(CH ₃) ₂ N	
363	3-SCH ₃	
10 364	2-F	
365	2-Cl	
366	2-Br	
367	2-I	
368	2-CH ₃ O	
15 369	2-CH ₃	
370	2-CH ₂ OH	
371	2-CF ₃	
372	2-CH ₂ NH ₂	
373	2-NH ₂	
20 374	3,4-F ₂	
375	3,4-Cl ₂	
376	3,4-(CH ₃ O) ₂	
377	2,4-Cl ₂	
378	2,4-F ₂	
25 379	2,4-(CH ₃ O) ₂	
380	3,5-F ₂	
381	3,4-Cl ₂	
382	3,4-(CH ₃) ₂	
383	2,4-(NH ₂) ₂	
30 384	3,4-(NH ₂) ₂	
385	4-(CH ₃ O)-3-NH ₂	
386	3,4-OCH ₂ O	
387	F ₅	
388	Cl ₅	
35 389	3,4,5-(CH ₃ O) ₃	

Footnote for Table 8

- (a) bp 115-137°C (0.3 mm Hg); $^1\text{H-NMR}$: 7.33-7.06 (m, 2H),
7.03-6.97 (m, 2H), 4.45 (s, 2H), 3.32 (d, 2H, $J=6$);
HRMS: Calcd for $\text{C}_{17}\text{H}_{24}\text{FNO}$: 277.1842; Found:
5 277.1829; Anal.: Calcd for $\text{C}_{17}\text{H}_{24}\text{FNO}$: C, 73.61, H,
8.72, N, 5.05; Found: C, 72.68, 72.51, H, 9.27,
8.98, N, 4.66, 4.96.

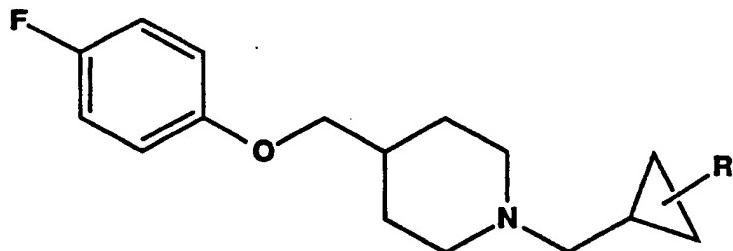
54

Table 9

5

	<u>Ex.</u>	<u>Ar</u>	<u>mp (°C)</u>
	390	2-naphthyl	
	391	1-naphthyl	
	392	2-quinolinyl	
10	393	4-quinolinyl	
	394	2-pyridyl	
	395	3-pyridyl	
	396	4-pyridyl	
	397	2-pyrimidyl	
15	398	2-furyl	
	399	2-thienyl	

55
Table 10



	<u>Ex.</u>	<u>R</u>	<u>mp (°C)</u>
	400	1-CH ₃	
	401	2-CH ₃	(a)
	402	2,2-Cl ₂ -1-CH ₃	(b)
	403	2,2-(CH ₃) ₂ -3-(CH=C(CH ₃) ₂)	
10	404	2,2-(CH ₃) ₂ -3(CH=CCl ₂)	
	405	2,2-Cl ₂	
	406	2-F	
	407	2-Cl	
	408	1-OH	
15	409	2,2,3,3-(CH ₃) ₄	

Footnotes for Table 10

(a) ¹H-NMR (CDCl₃, 300 MHz): 6.95 (t, 2H, J=8), 6.8 (dd, 2H, J=8, 6), 3.75 (d, 2H, J=7), 3.2-3.0 (m, 2H), 2.45 (dd, 1H, J=9, 6), 2.15 (dd, 1H, J=9, 7), 2.1-1.9 (m, 2H), 1.9-1.7 (m, 3H), 1.55-1.4 (m, 2H), 1.05 (d, 3H, J=7), 1.65-1.45 (m, 2H), 0.25 (t, 2H, J=7); Calcd for C₁₇H₂₄FNO: 277.1842; Found: 277.1818.

(b) ¹H-NMR (CDCl₃, 300 MHz): 7.0-6.9 (m, 2H), 6.9-6.8 (m, 2H), 3.75 (d, 2H, J=7), 3.0-2.9 (m, 2H), 2.55 (dd, 2H, J=12, 6), 2.1-1.95 (m, 2H), 1.9-1.7 (m, 4H), 1.4 (s, 3H), 1.5-1.3 (m, 1H), 1.25 (s, 2H); HRMS: Calcd for C₁₇H₂₂FCl₂NO: 345.1063; Found: 345.1064.

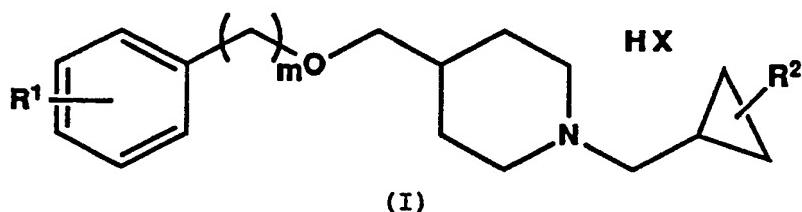
56

Example 4101-(Cyclopropylmethyl)-4-(4'-Fluorophenoxyethyl)-
piperidine Hydrochloride Salt

A solution of 1-(cyclopropylmethyl)-4-(4'-fluorophenoxyethyl)piperidine (250 mg, 0.95 mmol) in ether (5 mL) was stirred at room temperature. A 1 N hydrogen chloride-ether solution (5 mL) was added dropwise. The precipitate was filtered and washed with copious amounts of ether. Drying in vacuo at 60°C afforded a white powder (200 mg): mp 162-164°C; ¹H-NMR (DMSO-d₆): 10.6-10.2 (m, 1H), 7.35-6.85 (m 5H), 3.9 (d, 2H, J=7), 3.6-3.4 (m, 1H), 3.35-3.1 (m, 2H), 3.05-2.75 (m, 3H), 2.1-1.5 (m, 4H), 1.2-1.0 (m, 2H), 0.7-0.55 (m, 2H), 0.25-0.1 (m, 2H); Anal.: Calcd for C₁₆H₂₃FNO·HCl: C, 63.88, H, 8.04, N, 4.66, F, 6.32, Cl, 11.79; Found: C, 64.08, H, 7.84, N, 4.58, F, 6.10, Cl, 11.96.

The compounds of Table 11 can be prepared using the process described in Example 410, employing the appropriate acid.

5

Table 11

	<u>Ex.</u>	<u>m</u>	<u>R¹</u>	<u>R²</u>	<u>HX</u>	<u>mp (°C)</u>
10	410	0	4-F	H	HCl	162-164
	411	0	4-Cl	H	HCl	145-146 (a)
	412	0	4-CH ₃ O	H	HCl	125-127 (b)
	413	0	3,4,5-(CH ₃ O) ₃	H	HCl	113-114 (c)
15	414	0	4-CH ₂ OH	H	HCl	
	415	0	H	H	HCl	
	416	1	F	H	HCl	123-125 (d)
	417	1	4-CH ₃ O	H	HCl	
	418	0	3-(CH ₃) ₂ N	H	HCl	
20	419	3	F	H	HCl	
	420	0	4-CH ₃ S	H	HCl	157-158 (e)
	421	0	3,4-F ₂	H	HCl	151-152 (f)
	422	0	4-EtNH	H	HCl	130-133 (g)
	423	0	F ₅	H	HCl	173-174 (h)
25	424	0	4-F	2,2-Cl ₂ - 1-CH ₃	maleate	156-157 (i)
	425	0	4-F	2-CH ₃	fumarate	115-117 (j)

Footnotes for Table 11

- 30 (a) Anal.: Calcd for C₁₆H₂₁ClNO·HCl: C, 60.96, H, 7.03, N, 4.44, Cl, 22.49; Found: C, 60.85, H, 7.30, N, 4.43, Cl, 22.53.

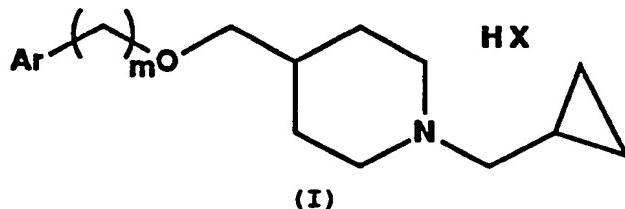
Footnotes for Table 11 (continued)

- (b) Anal.: Calcd for $C_{17}H_{25}NO_2 \cdot HCl \cdot 0.25H_2O$: C, 64.54, H, 8.44, N, 4.43, Cl, 11.20; Found: C, 64.53, 64.54, H, 8.43, 8.50, N, 4.32, 4.44, Cl, 11.58, 11.58.
- 5 (c) 1H -NMR (DMSO-d₆): 10.9-10.6 (m, 1H), 6.25 (s, 2H), 5.5-5.1 (m, 2H), 3.9-3.5 (m, 5H), 2.75 (s, 6H), 3.55 (s, 3H), 3.1-2.8 (m, 4H), 2.1-1.6 (m, 4H), 1.2-1.0 (m, 1H), 0.7-0.55 (m, 2H), 0.45-0.3 (m, 2H); Anal. Calcd for $C_{19}H_{29}NO_4 \cdot 1.3 HCl$: C, 59.61, H, 7.97, N, 3.66, Cl, 12.04; Found: C, 59.31, 59.18, H, 8.10, 8.07, N, 3.50, 3.53, Cl, 11.67, 11.64.
- (d) Anal.: Calcd for $C_{17}H_{24}FNO \cdot HCl$: C, 65.06, H, 8.03, N, 4.46; Found: C, 65.16, 64.98, H, 8.18, 8.29, N, 4.29, 4.12.
- 10 (e) Anal.: Calcd for $C_{17}H_{25}NOS \cdot HCl$: C, 62.27, H, 7.68, N, 4.27, S, 9.78, Cl, 10.81; Found: C, 62.30, H, 7.91, N, 4.17, S, 9.59, Cl, 10.83.
- (f) Anal.: Calcd for $C_{16}H_{21}F_2NO \cdot HCl$: C, 60.47, H, 6.66, N, 4.41, F, 11.96, Cl, 11.16; Found: C, 60.43, H, 6.78, N, 4.25, F, 11.98, C, 10.91.
- 15 (g) Anal.: Calcd for $C_{18}H_{28}N_2O \cdot 2HCl \cdot 0.5H_2O$: C, 58.37, H, 8.44, N, 7.56; Found: C, 58.24, 58.50, H, 9.07, 8.74, N, 7.07, 6.96.
- (h) Anal.: Calcd for $C_{16}H_{18}F_5NO \cdot HCl$: C, 51.69, H, 5.15, N, 3.76, F, 25.55, Cl, 9.54; Found: C, 51.60, H, 5.07, N, 3.97, F, 25.54, Cl, 9.39.
- 20 (i) Anal.: Calcd for $C_{17}H_{22}FCl_2NO \cdot C_4H_4O_4$: C, 54.56, H, 5.66, N, 3.03, Cl, 15.34, F, 4.11; Found C, 54.47, H, 5.67, N, 3.02, Cl, 15.00, F, 4.10.
- 25 (j) Anal.: Calcd for $C_{17}H_{24}FNO \cdot C_4H_4O_4$: C, 61.75, H, 6.91, N, 3.43, F, 4.65; Found: C, 62.28, 62.15, H, 7.03, 7.04, N, 3.40, 3.38, F, 4.24, 4.09.

The compounds of Table 12 can be prepared using the process described in Example 410, employing the appropriate acid.

Table 12

5



<u>Ex.</u>	<u>m</u>	<u>Ar</u>	<u>HX</u>	<u>mp. (°C)</u>
10	426	0	2-naphthyl	HCl 206-208 (a)
	427	0	4-pyridyl	HCl
	428	0	4-quinolinyl	HCl

Footnote for Table 12

15 (a) Anal.: Calcd for C₂₀H₂₅NO·HCl: C, 72.38, H, 7.90, N, 4.22, Cl, 10.68; Found: C, 72.27, H, 8.09, N, 4.14.

60

Example 429 describes an alternate procedure to prepare the product of Example 1.

Example 429

5

Synthesis of 1-(cyclopropylmethyl)-4-(4'-Fluorophenoxy)methyl)piperidine

A. Ethyl 1-(Cyclopropylcarbonyl)piperidine-4-carboxylate

(1) A solution of ethyl isonipecotate (65 g, 413 mmol) and pyridine (65.3 g, 66.8 mL, 826 mmol) in ether (500 mL) was stirred at about 0°C under a nitrogen atmosphere. A solution of cyclopropyl-carboxylic acid chloride (43.2 g, 37.5 mL, 413 mmol) in ether (500 mL) was added dropwise over 30 minutes. The reaction mixture was stirred while warming gradually to room temperature over 21 hours, then it was poured onto water (1 L) and mixed. The layers were separated; the organic layer was washed once with a 1 N hydrochloric acid solution (1 L), then twice with a saturated sodium bicarbonate solution (1 L). The organic solution was dried over magnesium sulfate and filtered. Solvent was removed in vacuo to give a clear pale yellow liquid. Vacuum distillation (bp 140-145°C, 0.4 mm Hg) afforded a clear colorless liquid (45 g, 48% yield): ¹H-NMR: 4.5-4.25 (m, 1H), 4.15 (q, 2H, J=7), 3.35-3.05 (m, 1H), 2.96-2.7 (m, 1H), 2.65-2.45 (m, 1H), 2.0-1.85 (m, 2H), 1.75-1.5 (m, 3H), 1.25 (t, 3H, J=7), 1.0-0.9 (m, 2H), 0.75-0.6 (m, 2H); HRMS: Calcd for C₁₂H₁₉NO₃:225.1365; Found: 225.1365.

(2) Alternatively, this compound can be made as follows: Ethyl isonipecotate (48 mL, 0.31 mole), (bromomethyl)cyclopropane (85%, 50 g, 0.31 mole), and potassium carbonate (48 g, 0.35 mole) were stirred at room temperature in dry ethyl alcohol (500 mL) for 23 hours. The mixture was filtered through Celite®, rinsed

with ethyl acetate and concentrated in vacuo. The resulting mixture was diluted with ethyl acetate (1 L), extracted with H₂O (2 x 250 mL), dried (MgSO₄) and concentrated in vacuo. The crude product was distilled, 5 bp 90-115°C at 0.8 mm Hg, to yield the product (33.8 g, 52%) as a colorless oil, which gave ¹H-NMR and MS data as listed above in Example 420 A (1).

B. 1-(Cyclopropylmethyl)-4-hydroxymethyl piperidine

10 (1) A solution of lithium aluminum hydride in tetrahydrofuran (1 M, 54.6 mL, 54.6 mmol) was added to tetrahydrofuran (100 mL) via syringe with stirring under a nitrogen atmosphere. This solution was cooled to 0 to 5°C. A solution of ethyl 1-(cyclopropyl-methyl) 15 piperidine-4-carboxylate (11.5 g, 55 mmol) in tetrahydrofuran (100 mL) was added dropwise over 15 minutes. The reaction mixture was heated to reflux temperature and stirred for 4 hours. The mixture was cooled to ambient temperature and ethyl acetate (100 mL) 20 was added dropwise, followed by water (20 mL). The resulting suspension was filtered through Celite®. The filtrate was concentrated in vacuo. Vacuum distillation (bp 100°C, 0.1 mm Hg) afforded the product (6.15 g): ¹H-NMR: 3.5 (d, 2H, J=7), 3.1 (d, 2H, J=7), 2.4 (d, 2H, 25 J=7), 2.1-1.6 (m, 6H), 1.55-1.45 (m, 3H), 0.95-0.85 (m, 1H), 0.55-0.45 (m, 2H), 0.25-0.15 (m, 2H); HRMS: Calcd for C₁₀H₁₉NO: 169.1467; Found: 169.1467.

(2) Alternatively, this compound can be made as follows: Lithium aluminum hydride (8.55 g, 0.225 mole) 30 was added portionwise over 1 hour to a 0°C solution of the ester from Step A above (47.6 g, 0.225 mole) in dry Et₂O (500 mL). After 1.5 hours, the reaction was carefully quenched with H₂O (100 mL), then filtered through Celite® and rinsed with Et₂O. The filtrate was 35 diluted to 1 L total volume with Et₂O, and the phases

were separated. The organic phase was extracted with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was distilled, bp 108-127°C at 1.2 mm Hg, to yield the product as a colorless oil (29.3 g, 77%), which gave 1H -NMR and MS data as listed above in Example 420 B (1).

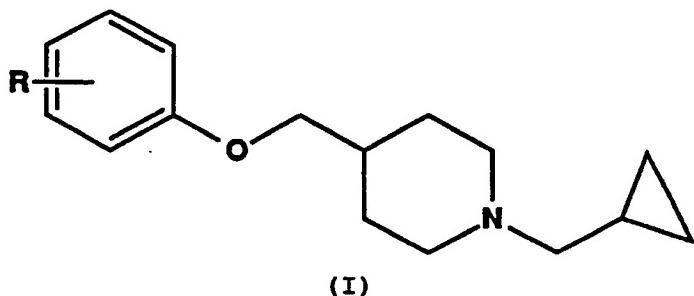
C. 1-(Cyclopropylmethyl)-4-(4'-Fluorophenoxy-methyl)piperidine

A solution of 4-fluorophenol (4.08 g, 36.4 mmol), 1-(cyclopropylmethyl)-4-hydroxymethyl-piperidine (6.15 g, 36.4 mmol) from Step B (1) or (2), and triphenylphosphine (14.43 g, 55 mmol) in benzene (100 mL) was stirred with ice-water bath cooling. Diethyl azodicarboxylate (9.58 g, 8.7 mL, 55 mmol) was added dropwise via syringe. The reaction mixture was heated to reflux and stirred for about 72 hour. The mixture was cooled to ambient temperature and solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (200 mL), and the organic solution was washed twice with water (100 mL) then twice with a 2 N sodium hydroxide solution (100 mL). Drying over magnesium sulfate, filtration and removal of solvent *in vacuo* gave a solid. Column chromatography using a gradient elution system (chloroform:methanol::95:5 to 4:1) afforded the product 740 mg, 8% yield, mp 34-36°C which gave 1H -NMR and MS data identical to that for the product from Example 1D.

63

The compounds of Table 13 may be prepared using the procedure described for Example 429, employing the appropriate phenol.

5

Table 13

	<u>Ex.</u>	<u>R</u>	<u>mp (°C)</u>
10	429-C	4-F	34-36
	430	4-NO ₂	68-70
	431	4-CO ₂ CH ₃	
	432	4-CON(CH ₃) ₂	
15	433	4-CN	109-111(a)

Footnote for Table 13

(a) See also Example 515

Example 434 and subsequent examples describe the preparation of additional compounds of formula (I) (where X = CO or CHO).

5

Example 434

Synthesis of 1-(Cyclopropylmethyl)-4-(2'-(4"-fluorophenyl)-2'-oxoethyl)piperidine

A. (1) 1-(4'-fluorophenyl)-2-(4''-pyridyl)ethanone

10 A solution of di-isopropylamine (4.44 g, 6.16 mL, 44 mmol) in anhydrous tetrahydrofuran (50 mL) was cooled to about 0°C with stirring in a flame-dried flask under a nitrogen atmosphere. A solution of n-butyl lithium in hexane (2.5 M, 17.6 mL, 44 mmol) was added dropwise, then the reaction mixture was stirred at about 0°C for 15 minutes. A solution of 4-picoline (3.92 g, 40 mmol) in anhydrous tetrahydrofuran (50 mL) was added dropwise, then the reaction mixture was stirred at about 0°C for about 15 minutes.

15 A solution of ethyl 4-fluorobenzoate (6.73 g, 5.87 mL, 40 mmol) in tetrahydrofuran (100 mL) was stirred at about 0°C under a nitrogen atmosphere. The pyridinemethyl lithium solution, prepared above was added dropwise via a canula. The reaction mixture was then stirred while being warmed to ambient temperature 25 for about 3 hours. The reaction mixture was then poured onto a 2 N sodium hydroxide solution (200 mL) and extracted with ethyl acetate three times. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo.

30 Column chromatography of the residue with ethyl acetate gave the product, a yellow solid (1.0 g, R_f = 0.2): mp 90-93°C; ¹H-NMR: 8.65-8.5 (m, 2H), 8.05 (dd, 2H, J=8,6), 7.25-7.1 (m, 4H), 4.3 (s, 2H); MS:215; IR (KBr): 1684(s), 1596(s), 1505(m), 1417(m).

65

The column was eluted with ethyl acetate-methanol (4:1) to give, after removal of solvent in vacuo, a glassy solid, 4-fluorophenyl bis-(4-pyridylmethyl) methanol (1.1 g): mp 35-36°C; ¹H-NMR: 8.2 (d, 4H, J=6), 7.25 (dd, 2H, J=8, 6), 7.0 (dd, 2H, J=7), 6.85 (d, 2H, J=6), 3.8-3.6 (m, 1H), 3.2 (q, 4H, J=10); MS: 308; IR(KBr): 3420 (br, s), 2928 (m), 1603 (s), 1560 (m), 1510 (s), 1419 (s); Anal.: Calcd for C₁₉H₁₇FNO•0.5•H₂O: C, 71.91, H, 5.72, N, 8.83; Found: C, 71.75, 72.00, H, 5.60, 5.64, N, 8.44, 8.61.

Alternatively, Step 434 A(2) may be used to make an appropriate intermediate.

A. (2) 1-(4'-Fluorophenyl)-2-(4'-pyridyl)ethanone

A solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (1 M, 400 mL, 0.4 mol) was cooled to about 0°C with stirring under a nitrogen atmosphere. A solution of 4-picoline (37.25 g, 38.9 mL, 0.4 mol) in anhydrous tetrahydrofuran (560 mL) was added dropwise over 30 minutes. The reaction mixture was stirred at 0-10°C for 30 minutes.

A solution of ethyl 4-fluorobenzoate (33.6 g, 29.3 mL, 0.2 mol) in anhydrous tetrahydrofuran (400 mL) was cooled to about 0°C with stirring under a nitrogen atmosphere. The above solution of 4-pyridinemethyl sodium was added dropwise via an additional funnel such that the internal temperature did not exceed 15°C. The reaction mixture was then stirred at ambient temperature for about 3 hours. The reaction mixture was poured onto water (1 L) and extracted three times with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. Vacuum distillation (bp 140°C, 0.1 mm Hg) gave the product (25.3 g), which solidified on cooling and which

was identical in all respects to the product from Example 434 A(1).

B. 1-(Cyclopropylmethyl)-4-(2'-(4''-fluorophenyl)-2'-oxoethyl)pyridinium bromide

5 A mixture of 1-(4''-fluorophenyl)-2-(4'-pyridyl)-ethanone from Step A(1) or A(2) above (5 g, 23.3 mmol) and bromomethyl cyclopropane (18.8 g, 13.5 mL, 140 mmol) was stirred at reflux temperature under a nitrogen
10 atmosphere for about 1 hour. A pale yellow solid formed upon cooling to ambient temperature. Filtration and trituration with copious amounts of ether afforded a pale yellow solid: ¹H-NMR: 9.45 (d, 2H, J=6), 8.35-8.0 (m, 4H), 7.2 (br t, 2H, J=7), 5.0-4.8 (m, 4H), 1.65-1.4 (m, 1H), 0.85-0.65 (m, 4H).

C. 1-(Cyclopropylmethyl)-4-(2'-(4''-fluorophenyl)-2'-oxoethyl)piperidine

20 Platinum dioxide (1 g) was suspended in degassed ethanol (100 mL) and this suspension was stirred under a hydrogen atmosphere until hydrogen uptake ceased. A solution of 1-(cyclopropylmethyl)-4-(2'-(4''-fluorophenyl)-2'-oxoethyl)pyridinium bromide from Step B above, (7.9 g) in degassed ethanol (200 mL) was added
25 and the mixture was stirred under a hydrogen atmosphere. After the theoretical amount of hydrogen had been taken up, the suspension was filtered through Celite®. Solvent was removed in vacuo to give the product as its hydrobromide salt, a white solid.
30 This solid was dissolved in water; the solution was basified with a 2 N sodium hydroxide solution, then extracted with chloroform three times. The combined organic layers were dried over magnesium sulfate and filtered. Solvent was removed in vacuo. Column
35 chromatography (chloroform:methanol::9:1) gave the

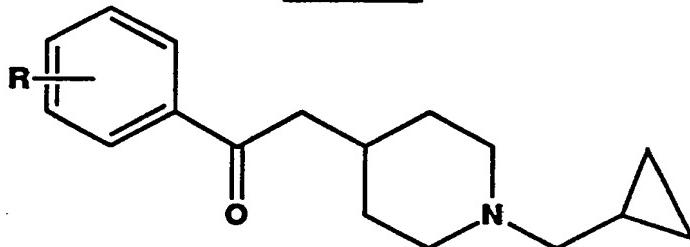
67

product, a pale yellow solid ($R_f=0.25$, 2.83 g): mp 73-75°C; IR (KBr): 3072 (w), 3006 (w), 2995 (w), 2943 (s), 2903 (s), 2840 (w), 2806 (w), 1679 (s), 1594 (s), 1504 (s), 1462 (s), 1448 (w), 1427 (w), 1410 (s); $^1\text{H-NMR}$: 8.0 (dd, 2H, $J=8, 6$), 7.15 (br t, 2H, $J=8$), 3.1 (br d, 2H, $J=9$), 2.9 (d, 2H, $J=7$), 2.35 (d, 2H, $J=7$), 2.1-1.6 (m, 6H), 1.55-1.35 (m, 2H), 1.0-0.8 (m, 1H), 0.65-0.4 (m, 2H), 0.25-0.0 (m, 2H); MS:275; Anal.: Calcd for $\text{C}_{17}\text{H}_{22}\text{FNO} \cdot 0.25 \cdot \text{H}_2\text{O}$: C, 72.96, H, 8.10, N, 5.00, F, 6.78; Found: C, 73.16, 72.99, H, 8.10, 8.06, N, 5.11, 5.13, F, 6.58, 6.52.

68

The compounds of Table 14 may be prepared using, in sequence, the procedures described in Examples 434 A(1) or A(2), B and C starting with the appropriate benzoate ester.

5

Table 14

	<u>Ex.</u>	<u>R</u>	<u>Salt</u>	<u>mp (°C)</u>
10	434	4-F		73-75
	435	4-Cl	HBr	154-155 (a)
	436	4-Br		
	437	4-I		
	438	H		
	15	4-N(CH ₃) ₂		104-106 (b)
15	439	4-NHCOCH ₃		
	440	4-NH ₂		
	441	4-OCH ₃	HBr	167-168 (c)
	442	4-OTBDMS		
	443	4-OC ₂ H ₅		(d)
	20	444		
20	444	4-SCH ₃		
	445	4-SC ₂ H ₅		
	446	4-CH ₂ NH ₂		
	447	3,5-(CF ₃) ₂		
	448	4-CH ₃		
	25	449		
25	450	4-C ₂ H ₅		
	451	4-CF ₃		35-36 (e)
	452	3-Cl		
	453	2-Cl		
	30	454		
		3-Br		

69

Table 14 (continued)

<u>Ex.</u>	<u>R</u>	<u>Salt</u>	<u>mp (°C)</u>
455	2-Br		
456	3-I		
5	457	2-I	
	458	3-N(CH ₃) ₂	
	459	3-NHCOCH ₃	
	460	3-NH ₂	
	461	3-OCH ₃	
	462	3-OTBDMS	
10	463	3-OC ₂ H ₅	
	464	3-SCH ₃	
	465	3-CH ₂ NH ₂	
	466	3-CH ₂ N(CH ₃) ₂	
	467	3-CF ₃	
15	468	2-Cl-5-Br	
	469	3-Br-4-CH ₃	
	470	4-t-C ₄ H ₉ O	
	471	4-t-C ₄ H ₉	HBr
			142-144 (f)
20	472	2-Cl-4-F	
	473	3-Cl-4-F	
	474	3-Cl-4-OTBDMS	
	475	4-Cl-2-OCH ₃	
	476	3-Cl-4-CH ₃	
25	477	2-Cl-5(CH ₃ S)	
	478	2-Cl-4-(NH ₂)	
	479	4-Cl-3-NH ₂	
	480	3,5-Br ₂ -4-OTBDMS	
	481	3,4-Cl ₂	
30	482	2,4-Cl ₂	
	483	3,5-Cl ₂	
	484	2,5-Cl ₂	
	485	3,5-Cl ₂ -4-OTBDMS	
	486	3,4-(OC ₂ H ₅) ₂	
35	487	3,4-(OCH ₃) ₂	

70

Table 14 (continued)

<u>Ex.</u>	<u>R</u>	<u>Salt</u>	<u>mp (°C)</u>
488	3, 4-(OCH ₃) ₂		
489	4-(C ₂ H ₅) ₂ N		
5 490	3, 4-F ₂		
491	2, 4-F ₂		
492	3, 5-F ₂		
493	3, 4-(CH ₃) ₂		
494	3, 5-(CH ₃) ₂		
10 495	3, 5-(NH ₂) ₂		
496	3-CH ₃ O-4NH ₂		
497	F ₅		
498	Cl ₅		
499	2, 3, 4, 5-F ₄		
15 500	2, 3, 5-Cl ₂		
501	2, 3, 4-F ₃		
502	2, 4, 5-F ₃		
503	4-C ₆ H ₅	HBr	233-234 (g)

20 Footnotes for Table 14

- (a) ¹H-NMR (CDCl₃, 300 MHz): 7.88 (d, 2H, J=8), 7.45 (d, 2H, J=8), 3.77-3.68 (m, 2H), 3.02 (d, 2H, J=7), 2.90 (d, 2H, J=8), 2.85-2.71 (m, 2H), 2.40-1.97 (m, 5H), 1.59 (br m, 1H), 1.40-1.30 (m, 1H), 0.85-0.78 (m, 2H), 0.48-0.40 (m, 2H); Anal.: Calcd for C₁₇H₂₂ClNO·HBr: C, 54.78, H, 6.22, N, 3.76; Found: C, 54.50, H, 6.21, N, 3.85.
- (b) ¹H-NMR (CDCl₃, 300 MHz): 7.9 (d, 2H, J=9), 6.65 (d, 2H, J=9), 3.2 (br d, 2H, J=11), 3.1 (s, 6H), 2.85 (d, 2H, J=7), 2.4 (d, 2H, J=7), 2.3-1.95 (m, 4H), 1.9-1.7 (m, 2H), 1.7-1.45 (m, 2H), 1.1-0.9 (m, 1H), 0.7-0.6 (m, 2H), 0.3-0.1 (m, 2H), HRMS: Calcd for C₁₉H₂₈N₂O: 300.2202; Found: 300.2218; Anal.: Calcd

Footnotes for Table 14 (continued)

for C₁₉H₂₈N₂O•0.5•H₂O: C, 73.75, H, 9.28, N, 9.05;

Found: C, 73.22, H, 9.05, N, 8.87.

(c) ¹H-NMR (CDCl₃, 300 MHz): 7.91 (d, 2H, J=8), 6.94 (d, 2H, J=8), 3.91 (s, 3H), 3.76-3.68 (m, 2H), 2.95 (d, 2H, J=7), 2.90 (d, 2H, J=7), 2.85-2.75 (m, 2H), 2.40-2.15 (m, 3H), 2.05-1.95 (m, 2H), 1.60 (br m, 1H), 1.40-1.31 (m, 1H), 0.84-0.77 (m, 2H), 0.50-0.43 (m, 2H); Anal.: Calcd for C₁₈H₂₅NO₂•HBr: C, 58.70, H, 7.12, N, 3.80; Found: C, 58.75, 58.54, H, 7.19, 7.14, N, 3.81, 3.81.

(d) ¹H-NMR (CDCl₃, 300 MHz): 7.85 (br d, 2H, J=8), 6.85 (br d, 2H, J=8), 3.05 (br d, 2H, J=10), 2.85 (d, 2H, J=7), 2.25 (d, 2H, J=7), 2.1 (br t, 3H, J=7), 1.85-1.7 (m, 2H), 1.5-1.3 (m, 2H), 1.0 (s, 9H), 0.95-0.8 (m, 2H), 0.55-0.45 (m, 2H), 0.25 (s, 6H), 0.15-0.05 (m, 2H); HRMS: Calcd for C₂₃H₃₇NO₂Si: 387.2594; Found: 387.2591.

(e) ¹H-NMR (CDCl₃, 300 MHz): 8.05 (d, 2H, J=8), 7.75 (d, 2H, J=8), 3.1 (br d, 2H, J=10), 2.95 (d, 2H, J=7), 2.3 (d, 2H, J=7), 2.2-1.95 (m, 3H), 1.9-1.7 (m, 2H), 2.6-2.35 (m, 2H), 1.0-0.8 (m, 1H), 0.6-0.45 (m, 2H), 0.2-0.05 (m, 2H); HRMS: Calcd for C₁₈H₂₂F₃NO: 325.1676; Found: 325.1652; Anal.: Calcd for C₁₈H₂₂F₂NO•0.25•H₂O: C, 65.54, H, 6.87, N, 4.24, F, 17.27; Found: C, 65.57, 65.52, H, 6.89, 6.89, N, 4.31, 4.36, F, 17.34.

(f) ¹H-NMR (CDCl₃, 300 MHz): 7.89 (d, 2H, J=8), 7.49 (d, 2H, J=8), 3.77-3.69 (m, 2H), 3.02 (d, 2H, J=6), 2.90 (d, 2H, J=8), 2.84-1.30 (m, 9H), 1.35 (s, 9H), 0.85-0.78 (m, 2H), 0.48-0.41 (m, 2H); HRMS: Calcd for C₂₁H₂₁NO: 313.2406; Found: 313.2405; Anal.: Calcd for C₂₁H₃₁NO•HBr•0.5 H₂O: C, 62.52, H, 8.25, N, 3.47; Found: C, 62.70, 62.47, H, 8.00, 7.94, N, 3.34, 3.33.

Footnotes for Table 14 (continued)

(g) $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): 8.03 (d, 2H, $J=8$), 7.70 (d, 2H, $J=8$), 7.65-7.40 (m, 5H), 3.78-3.69 (m, 2H), 3.08 (d, 2H, $J=7$), 2.90 (d, 2H, $J=8$), 2.87-2.75 (m, 2H), 2.43-1.98 (m, 5H), 1.58 (br m, 1H), 1.43-1.32 (m, 1H), 0.95-0.87 (m, 2H), 0.49-0.41 (m, 2H);
Anal.: Calcd for $\text{C}_{23}\text{H}_{25}\text{NO} \cdot \text{HBr}$: C, 66.66, H, 6.81, N, 3.38; Found: C, 66.23, 66.22, H, 6.86, 7.08; N, 3.41, 3.42.

10

Example 5041-(Cyclopropylmethyl)-4-2'-(4'''-Fluorophenyl)-2-oxoethyl-piperidine, hydrobromide salt

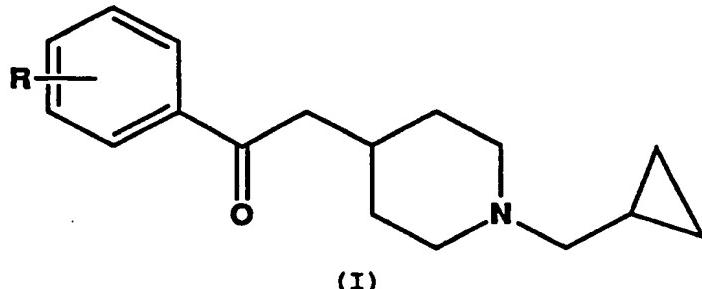
A mixture of 1-(cyclopropylmethyl)-4-(2'-(4'''-fluorophenyl)-2-oxoethyl)piperidine (24.1 g, 87.6 mmol), a hydrobromic acid solution (0.4 M, 62 ml) and ethanol (50 mL) was stirred with gentle heating until all solid dissolved. Solvent was removed in vacuo with gentle heating to give a white solid. The solid was suspended in a 2-propanol and mixed; again solvent was removed in vacuo with gentle heating to give a white solid. Trituration with ether and filtration gave the product. Drying in vacuo at about 60°C in a drying oven gave a white powder. (25.9 g): mp 141-143°C; IR (KBr): 3067 (w), 3038 (w), 2986 (m), 2939 (s), 2921 (s), 2702 (s), 2645 (s), 2592 (s), 2567 (s), 2520 (s), 1683 (s), 1601 (s), 1509 (s), 1470 (m), 1459 (s), 1436 (s), 1412 (s); $^1\text{H-NMR}$ (DMSO-d_6): 9.5-9.2 (m, 1H), 8.2-8.0 (br t, 2H, $J=7$), 7.4 (br t, 2H, $J=7$), 3.6-2.8 (m, 8H), 2.25-1.4 (m, 4H), 1.25-1.0 (m, 1H), 0.7-0.5 (m, 2H), 0.45-0.3 (m, 2H); Anal.: Calcd for $\text{C}_{17}\text{H}_{22}\text{FNO} \cdot \text{HBr}$: C, 57.31, H, 6.51, N, 3.93, F, 5.33, Br, 22.43; Found: C, 57.57, H, 6.65, N, 3.86, F, 5.15, Br, 22.16.

73

The compounds of Table 15 may be prepared by the procedure for Example 504 using the appropriate acid.

Table 15

5



<u>Ex.</u>	<u>R</u>	<u>Salt</u>	<u>mp (°C)</u>
10	4F	HBr	141-143
	4-CF ₃	HCl	140-142 (a)
506	4-N(CH ₃) ₂	HBr	113-115 (b)

Footnotes for Table 15

- 15 (a) Anal.: Calcd for C₁₈H₂₂F₃NO·HCl·0.5H₂O: C, 58.29, H, 6.52, N, 3.77, F, 15.27, Cl, 9.56; Found: C, 58.49, 58.22, H, 6.34, 6.33, N, 3.84, 3.80, F, 15.24, 15.32, Cl, 9.50, 9.28.
 (b) Anal.: Calcd for C₁₉H₂₈N₂O·2HBr·0.5H₂O: C, 48.42, H, 6.63, N, 5.94, Br, 33.91; Found: C, 48.83, 48.73, H, 6.89, 6.76, N, 5.65, 5.44, Br, 33.10, 33.27.
- 20

74

Example 507

1-(Cyclopropylmethyl)-4-(2'-(4''-hydroxy-phenyl)-2'-oxoethyl)piperidine, hydrochloride salt

1-(Cyclopropylmethyl)-4-(2'-(4''-t-butyl-

5 dimethylsilyloxyphenyl)-2'-oxoethyl)piperidine (from Example 443 above) (250 mg, 1.02 mmol) was reacted with a solution of tetra-n-butylammonium fluoride in tetrahydrofuran (1 M, 3 mL, 3 mmol) for about 14.5 hours. Solvent was removed in vacuo. The residue was
10 dissolved in water; a 1 N hydrochloric acid solution was added until pH=7. Three extractions with ethyl acetate, drying over magnesium sulfate, filtration and concentration in vacuo gave a light brown oil.

The oil was dissolved in ether-ethanol (5 mL, 1:1
15 (v/v)). A solution of hydrogen chloride in ether (1 M, 5 mL, 5 mmol) was added with stirring. Solvent was removed in vacuo; the residue was triturated with acetone and filtered. Drying in vacuo gave a white solid (25 mg): mp 209-211°C; NMR (DMSO-d₆, 300 MHz):
20 10.4 (s, 1H), 7.9 (d, 2H, J=8), 6.85 (d, 2H, J=8), 3.55-3.45 (m, 1H), 3.0-2.8 (m, 1H), 1.95-1.85 (m, 2H), 1.7-1.5 (m, 2H), 1.15-1.0 (m, 1H), 0.7-0.6 (m, 2H), 0.45-0.35 (m, 2H); HRMS: Calcd for C₁₇H₂₃NO₂: 273.1729; Found: 273.1727.

25

Example 508

1-(Cyclopropylmethyl)-4-(4'-cyanophenoxy-methyl)piperidine

Sodium hydride (50% in oil, 0.48 g, 10 mmol) was
30 washed with hexanes twice (decanting the solvent each time) and suspended in N,N-dimethylformamide (20 mL) with stirring under a nitrogen atmosphere. A solution of 1-(cyclopropylmethyl)-4-(hydroxy-methyl)piperidine (Example 429B) (1.6 g, 9.5 mmol) in N,N-dimethylformamide (10 mL) was added dropwise. Gas

evolution occurred. 4-Fluorobenzonitrile (1.21 g, 10 mmol) was added, then the reaction mixture was stirred at 100°C for 17 hours. Water was added. The solvent was distilled in vacuo. The residue was taken up in

- 5 water, basified with a 1 N sodium hydroxide solution and extracted three times with ethyl acetate. The combined organic layers were dried over MgSO₄ and filtered.

Solvent was removed in vacuo to give a brown oil.

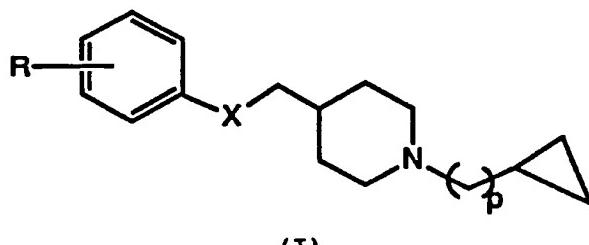
Column chromatography (chloroform: methanol::9:1)

- 10 gave a brown oil, after removal of solvent in vacuo. The oil was crystallized from ether-hexanes and filtered. Drying in vacuo afforded the product, a white powder (1.23 g): mp 109-111°C; IR (KBr): 3074 (w), 2997 (m), 2962 (w), 2939 (s), 2918 (s), 2883 (s), 2826 (s),
15 2779 (m), 2232 (s), 1607 (s), 1574 (m), 1511 (s); NMR CDCl₃, 300 MHz): 7.75 (d, 2H, J=8), 6.9 (d, 2H, J=8), 3.85 (d, 2H, J=7), 3.1 (br d, 2H, J=10), 2.25 (d, 2H, J=7), 2.0 (td, 2H, J=8), 1.9-1.75 (m, 3H), 1.5-1.35 (m, 2H), 0.9-0.8 (m, 1H), 0.55-0.45 (m 2, H), 0.15-0.05 (m, 2H); HRMS: Calcd for C₁₇H₂₂N₂O: 270.1732; Found: 270.1727; Anal.: Calcd for C₁₇H₂₂N₂O: C, 75.52, H, 8.20, N, 10.36; Found: C, 75.36, H, 8.35, N, 10.27.

76

The compounds in Table 16 may be prepared by the method described in Examples 1, 429 or 508 using the appropriate benzene derivative.

5

Table 16

<u>Ex.</u>	<u>R</u>	<u>X</u>	<u>p</u>	<u>Salt</u>	<u>mp (°C)</u>
509	4-F	S	1		(a)
510	4-F	NMe	1		
511	4-F	CHOH	1		114-116 (b)
512	4-NO ₂	O	1		68-70 (c)
513	4-F	NH	1		
514	1-tetrazole	O	1		
515	4-CN	O	1		109-111 (d)
516	4-COCH ₃	O	1		41-43 (e)
517	4-SO ₂ (OCH ₂ C ₆ H ₅)	O	1		
518	4-CO ₂ CH ₂ Ph	O	1		
519	4-CHO	O	1		
520	4-SO ₂ N(CH ₃) ₂	O	1		118-119 (f)
521	4-F	O	3		
522	4-F	C=O	0		
523	4-F	SO	1		(g)
524	4-F	SO ₂	1		73 (h)
525	4-F	C=O	2	HBr	108-109 (i)
526	4-F	O	2		(j)
527	4-F	O	2	fumarate	124-126 (k)

Footnotes for Table 16

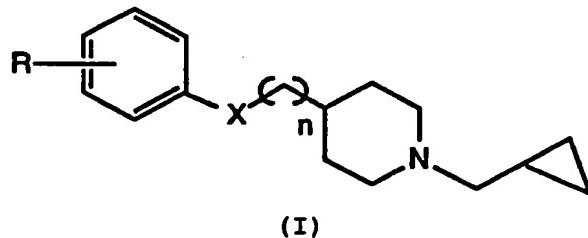
- (a) $^1\text{H-NMR}$ (CDCl_3 , 200 MHz): 7.3 (dd, 2H, $J=8, 6$), 7.0 (t, 2H, $J=8$), 3.1 (br d, 2H, $J=10$), 2.8 (d, 2H, $J=7$), 2.15 (d, 2H, $J=7$), 2.0-1.8 (m, 4H), 1.6-1.3 (m, 3H), 0.95-0.8 (m, 1H), 0.6-0.45 (m, 2H), 0.15-0.05 (m, 2H); HRMS: Calcd for $\text{C}_{16}\text{H}_{22}\text{FNS}$: 279.1457; Found: 279.1460.
- (b) Anal.: Calcd for $\text{C}_{17}\text{H}_{24}\text{FNO}$: C, 73.61, H, 8.72, N, 5.05, F, 6.84; Found: C, 72.64, 72.96, H, 8.77, 8.61, N, 5.00, 4.92, F, 6.86.
- (c) Anal.: Calcd for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_3 \cdot 0.75\text{H}_2\text{O}$: C, 63.26, H, 7.74, N, 9.22; Found: C, 63.14, 63.10, H, 7.40, 7.39, N, 9.35, 9.28.
- (d) Anal.: Calcd for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}$: C, 75.52, H, 8.20, N, 10.36; Found: C, 75.36, H, 8.35, N, 10.27. (See also Example 433).
- (e) Anal.: Calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_2$: C, 75.23, H, 8.77, N, 4.87; Found: C, 75.10, H, 8.87, N, 4.76.
- (f) Anal.: Calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_3\text{S}$: C, 61.33, H, 8.01, N, 7.95, S, 9.10; Found: C, 60.64, 60.64, H, 7.98, 7.94, N, 7.63, 7.64, S, 9.03.
- (g) Anal.: Calcd for $\text{C}_{16}\text{H}_{22}\text{FNO}_2\text{S}$: C, 61.71, H, 7.12, N, 4.49, F, 6.10, S, 10.30; Found: C, 61.57, H, 7.26, N, 4.39, F, 6.40, S, 10.36.
- (h) $^1\text{H-NMR}$ (CDCl_3 , 200 MHz): 7.65 (dd, 2H, $J=7, 2$), 7.25 (dd, 2H, $J=8, 2$), 3.1 (br t, 2H, $J=9$), 2.85 (dd, 1H, $J=10, 2$), 2.5 (dd, 1H, $J=10, 8$), 2.4-2.2 (m, 2H), 2.15-1.9 (m, 5H), 1.8-1.7 (m, 1H), 1.55-1.4 (m, 2H), 0.9-0.8 (m, 1H), 0.6-0.45 (m, 2H), 0.15-0.05 (m, 2H); HRMS: Calcd for $\text{C}_{16}\text{H}_{22}\text{FNOS}$: 295.1406; Found: 295.1409.
- (i) Anal.: for $\text{C}_{18}\text{H}_{24}\text{FNO} \cdot \text{HBR}$: C, 58.38, H, 6.53, N, 3.78, F, 5.13, Br, 21.57; C, 58.13, 58.35, H, 6.51, 6.38, N, 3.70, 3.61, F, 4.95, 4.93, Br, 21.59.

Footnotes for Table 16

- (j) $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): 6.9 (br t, 2H, $J=8$), 6.75
5 (dd, 2H, $J=8, 6$), 3.7 (d, 2H, $J=7$), 2.9 (br d, 2H,
 $J=9$), 2.5-2.35 (m, 2H), 2.0-1.85 (m, 2H), 1.85-1.65
(m, 3H), 1.5-1.3 (m, 4H), 0.7-0.5 (m, 1H), 0.45-0.3
10 (m, 2H), 0.1-0.0 (m, 2H); HRMS: Calcd for $\text{C}_{17}\text{H}_{24}\text{FNO}$:
277.1842; Found: 277.1837.
- (k) Anal.:Calcd for $\text{C}_{17}\text{H}_{24}\text{FNO} \cdot \text{C}_4\text{H}_4\text{O}_4$: C, 64.11, H, 7.17,
N, 3.56, F, 4.82; Found: C, 64.05, 64.30, H, 7.30,
7.41, N, 3.89, 3.90, F, 4.83, 4.85.

The compounds in Table 17 may be prepared by the method described in Example 1C using the appropriate hydroxy aromatic compound.

5

Table 17

Ex.	R	X	n	mp (°C)
10	528 529 530 531 532	O	1	
	4-piperidinyl 4-C ₆ H ₅ 4-C ₆ H ₅ O 4-C ₆ H ₅ S 4-(4'-FC ₆ H ₄)	O	1	62-63 (a)
		O	1	81-83 (b)
	533 534 535 536	O	1	122-123 (c)
	4-(4'-CH ₃ OC ₆ H ₄) 4-(4'-CH ₃ C ₆ H ₄) 4-(4'-CH ₃ SC ₆ H ₄) 4-(4'-CF ₃ C ₆ H ₄)	O	1	
	537	O	0	
	4-F	O	0	
20				

Footnotes for Table 17

(a) Anal.: Calcd for C₂₂H₂₇NO₂: C, 78.30, H, 8.06, N, 4.15; Found: C, 78.20, H, 8.12, N, 4.04.

(b) Anal.: Calcd for C₂₂H₂₆FNO: C, 77.84, H, 7.72, N, 4.13, F, 5.60; Found: C, 77.71, 77.71, H, 7.78,

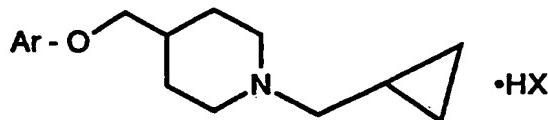
7.78, N, 3.93, 3.93, F, 3.77, 3.60.

(c) Anal.: Calcd for C₂₃H₂₉NO₂·0.5H₂O: C, 76.62, H, 8.39, N, 3.88; Found: C, 76.83, 76.86, H, 8.20, 8.17, N, 3.60, 3.58.

80

The compounds in Table 18 may be prepared by the methods described in Example 508 or 410, using the appropriate starting materials.

5

Table 18

<u>Ex.</u>	<u>Ar</u>	<u>HX</u>	<u>mp (°C)</u>
10 538	2-pyrimidyl		(a)
539	2-pyrimidyl	HCl	151-152 (b)
540	2-pyridyl		(c)
541	2-pyridyl	HCl	176-178 (d)

15 Footnotes for Table 18

- (a) ¹H-NMR (CDCl₃, 300 MHz): 8.45-8.35 (m, 2H), 6.85-6.8 (m, 1H), 4.1 (d, 2H, J=7), 3.05 (br d, 2H, J=10), 2.2 (d, 2H, J=7), 2.0-1.7 (m, 5H), 1.45-1.3 (m, 2H), 0.9-0.75 (m, 2H), 0.1-0.0 (m, 2H).
- (b) Anal.: Calcd for C₁₄H₂₁N₃O·1.3 HCl: C, 57.05, H, 7.62, N, 14.26, Cl, 15.64; Found: C, 56.18, 56.34, H, 7.51, 7.65, N, 13.95, 14.05, Cl, 15.05, 15.25.
- (c) ¹H-NMR (CDCl₃, 300 MHz): 8.05-8.0 (m, 1H), 7.5-7.35 (m, 1H), 6.8-6.7 (m, 1H), 6.65-6.55 (m, 1H), 4.05 (d, 2H, J=7), 3.05 (br d, 2H, J=10), 2.2 (d, 2H, J=7), 1.9 (br t, 2H, J=9), 1.8-1.6 (m, 3H), 1.5-1.3 (m, 2H), 0.9-0.7 (m, 1H), 0.5-0.35 (m, 2H), 0.1-0.0 (m, 2H); MS: 246.
- (d) Anal.: Calcd for C₁₅H₂₂N₂O·1.5 HCl: C, 56.52, H, 7.43, N, 8.78, Cl, 16.68; Found: C, 56.37, 56.18, H, 7.77, 7.76, N, 8.61, 8.44, Cl, 19.76, 19.66.

81

Example 5421-(Cyclopropylmethyl)-4-(2'-(4''-cyano-phenyl)-2'-oxoethyl)piperidine

A mixture of sodium cyanide (4.9 g, 100 mmol) and 5 1-(cyclopropylmethyl)-4-(2'-(4''-fluorophenyl)-2'-oxoethyl)piperidine (Example 434, 1.0 g, 3.6 mmol) in N,N-dimethylformamide (50 mL) was stirred at 120°C for 26 h. The excess solvent was distilled in vacuo; the residue was dissolved in water and extracted three times with 10 ethyl acetate. The combined organic layers were washed with water twice, dried over anhydrous magnesium sulfate and filtered. Solvent was removed in vacuo to give an oil.

Column chromatography (CHCl₃: MeOH::9:1) afforded 15 the product, a solid (0.68 g, 67% yield): mp 107-108°C; Anal.: Calcd for C₁₈H₂₂N₂O·0.25H₂O: C, 75.38, H, 7.90, N, 9.76; Found: C, 75.13, 74.97, H, 7.87, 7.96, N, 9.65, 9.52.

20

Example 5431-(Cyclopropylmethyl)-4-(2'-(4''-aminophenyl)-2'-oxoethyl)piperidine

Following the procedure of Example 542, sodium azide (6.5 g, 100 mmol) was reacted with the product of 25 Example 434 (1.0 g, 3.6 mmol) to afford the title compound, a solid (0.35 g): mp 140-146 (dec); MS:272; Anal.: Calcd for C₁₇H₂₂N₂O·0.75H₂O: C, 71.42, H, 8.99, N, 9.80; Found: C, 71.06, 71.03, H, 8.58, 8.54, N, 9.98, 9.99.

30

Example 5441-(Cyclopropylmethyl)-4-(4'-methylsulfonyl-phenoxyethyl)piperidine

A mixture of a 1 N NaOH solution (10 mL) and 35 1-(cyclopropylmethyl)-4-(4'-methylthiophenoxy-

82

methyl)piperidine, hydrochloride salt (Example 420, 0.5 g, 1.5 mmol) was stirred for 15 min and then extracted three times with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. Solvent was removed in vacuo.
5 The residue was taken up in a mixture of methanol (10 mL) and water (10 mL). Sodium periodate (2.13 g, 10 mmol) was added; the resulting suspension was stirred for 22 h. The reaction mixture was diluted with 250 mL
10 water, basified with 1 N NaOH solution and extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate and filtered. Solvent was removed in vacuo.

Column chromatography (CHCl₃:MeOH::9:1) of the residue afforded the title compound, a solid (0.29 g): mp 134-135°C; ¹H-NMR (CDCl₃, 300 MHz): 7.85 (d, 2H, J=8), 7.0 (d, 2H, J=8), 3.9 (d, 2H, J=7), 3.15 (br d, 2H, J=10), 3.05 (s, 3H), 2.3 (d, 2H, J=7), 2.1 (br t, 2H, J=7), 1.95-1.8 (m, 3H), 1.6-1.4 (m, 2H), 0.95-0.85
20 (m, 1H), 0.6-0.5 (m, 2H), 0.2-0.1 (m, 2H); HRMS: Calcd for C₁₇H₂₅NO₃S: 323.1555; Found: 323.1554.

Examples 545 and 546

25 1-(Cyclopropylmethyl)-4-(4'-fluorophenyl-sulfonylmethyl)piperidine (Example 545)
and 1-(cyclopropylmethyl)-4-(4'-fluorophenyl-sulfinylmethyl)piperidine (Example 546)

1-(Cyclopropylmethyl)-4-(4'-fluorophenylthio-
30 methyl)piperidine, hydrobromide salt (Example 509, hydrobromide salt, 1.0 g) was treated with a 1 N NaOH solution (50 mL); the mixture was extracted with ethyl acetate three times. The organic solution was dried over magnesium sulfate and filtered. Solvent was
35 removed in vacuo.

The residue was reacted with sodium periodate (7.7 g, 36 mmol) in methanol (30 mL) and water (30 mL for 21.5 h). The reaction mixture was diluted with water (500 mL), basified with a 1 N NaOH solution and extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate and filtered. Solvent was removed in vacuo.

Column chromatography (CHCl₃:MeOH::9:1) gave two products:

- 10 (1) (Cyclopropylmethyl)-4-(4'-fluorophenylsulfonylmethyl)piperidine (Example 545) R_f=0.3, 367 mg): mp 73°C; ¹H-NMR (CDCl₃, 200 MHz): 7.95 (dd, 2H, J=7,2), 7.25 (dd, 2H, J=8,2), 3.1-2.95 (m, 2H), 3.05 (d, 2H, J=7), 2.25 (d, 2H, J=7), 2.1-1.85 (m, 4H), 1.55-1.4 (m, 2H), 0.9-0.8 (m, 1H), 0.55-0.45 (m, 2H), 0.15-0.05 (m, 2H); Anal.: Calcd for C₁₆H₂₂FNO₂S: C, 61.71, H, 7.12, N, 4.49, F, 6.10, S, 10.30; Found: C, 61.57, H, 7.26, N, 9.39, F, 6.40, S, 10.36;
- 15 (2) 1-(cyclopropylmethyl)-4-(4'-fluorophenylsulfinylmethyl)piperidine (Example 546, R_f=0.17, 90 mg): ¹H-NMR (CDCl₃, 200 MHz): 7.65, (dd, 2H, J=7,2), 7.25 (dd, 2H, J=8,2), 3.1 (br t, 2H, J=9), 2.85 (dd, 1H, J=10,2), 2.5 (dd, 1H, J=10,8), 2.4-2.2 (m, 2H), 2.15-1.9 (m, 5H), 1.8-1.7 (m, 1H), 1.55-1.4 (m, 2H), 0.9-0.8 (m, 1H), 0.6-0.45 (m, 2H), 0.15-0.05 (m, 2H); HRMS: Calcd for C₁₆H₂₂FNOS: 295.1406; Found: 295.1409.

Example 547

- 30 1-(Cyclopropylmethyl)-4-(2'-(4''-fluorophenyl)-2'-phenyl-2'-hydroxyethyl)piperidine
- 1-(Cyclopropylmethyl)-4-(2'-(4''-fluorophenyl)-2'-oxoethyl)piperidine (Example 429, 1.0 g, 3.6 mmol) was mixed with dry tetrahydrofuran (10 mL). A solution of phenyl magnesium bromide in ether (3.0 M, 3 mL, 9 mmol) was added with stirring. The reaction mixture was

84

stirred for 24 h; poured onto a saturated NH₄Cl solution and extracted with ethyl acetate three times. The combined organic layers were dried over magnesium sulfate and filtered. Solvent was removed in vacuo.

- 5 Trituration with ether-hexanes (1:9) and filtration afforded the title compound, a solid, which was dried in vacuo. (1.0 g): mp 115-116°C; Anal.: Calcd for C₂₃H₂₈FNO: C, 77.36, H, 7.90, N, 3.92, F, 5.32; Found: C, 77.47, 77.41, H, 8.00, 7.92, N, 3.42, 3.52, F, 5.09.

10

Example 548

1-(Cyclopropylmethyl)-4-(2',2'-bis(4''-Fluorophenyl)-2-hydroxyethyl)piperidine

- Following the procedure described for Example 547, 15 the compound of Example 429 (1.0 g, 3.6 mmol) was reacted a solution of 4-fluorophenylmagnesium bromide in tetrahydrofuran (1.0 M, 9 mL, 9 mmol) to give the title compound, a solid (1.1 g): mp 119-121°C; Anal.: Calcd for C₂₃H₂₇F₂NO·0.5H₂O: C, 72.60, H, 7.41, N, 3.68, F, 20 9.99; Found: C, 72.89, 72.84, H, 7.14, 7.21, N, 3.29, 3.24, F, 9.82, 9.67.

Example 549

1-(Cyclopropylmethyl)-4-(2'-(4''-fluorophenyl)-2'-oxo-1'-benzylethyl)piperidine

- 25 A solution of the compound of Example 429 (1.0 g, 3.6 mmol) in dry tetrahydrofuran (25 mL) was stirred at 0°C. A solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (1 M, 4 mL, 4 mmol) was added and 30 stirring was continued for 40 min. Benzyl chloride (0.51 g, 0.46 mL, 4 mmol) was added; the reaction mixture was heated to reflux temperature and stirred for 23 h. The reaction mixture was cooled to ambient temperature, poured onto water, basified with a 1 N NaOH 35 solution and extracted with ethyl acetate three times.

85

The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. Column chromatography (CHCl₃:MeOH::9:1) gave the title compound (455 mg), a yellow oil: ¹H-NMR (CDCl₃, 200 MHz): 7.7 (4H), 7.2-7.0 (m, 5H), 7.0 (t, 2H, J=8), 3.65-3.55 (m, 1H), 3.2-2.9 (m, 4H), 2.25 (d, 2H, J=7), 2.0-1.7 (m, 4H), 1.65-1.4 (m, 3H), 0.9-0.75 (m, 1H), 0.55-0.45 (m, 2H), 0.15-0.05 (m, 2H); HRMS: Calcd for C₂₄H₂₈FNO: 365.2155; Found: 365.2156.

10

Example 5501-(Cyclopropylmethyl)-4-(4'-(5''-tetrazolyl)-phenoxyethyl)piperidine

A mixture of 1-(cyclopropylmethyl)-4-(4'-cyanophenoxy)methylpiperidine (Example 515, 0.75 g, 2.8 mmol), sodium azide (0.2 g, 3 mmol), ammonium chloride (0.15 g, 3 mmol) and N,N-dimethylformamide (10 mL) was stirred at 100-120°C for 23 h. The excess solvent was distilled in vacuo; the residue was suspended in water. A concentrated hydrochloride solution was added until pH=1. The solid formed was filtered, washed with water and dried in vacuo. The title compound (100 mg) had the following analytical data: ¹H-NMR (DMSO-d₆, 300 MHz): 7.9 (d, 2H, J=7), 7.0 (d, 2H, J=7), 3.95 (d, 2H, J=6), 3.45 (br d, 2H, J=9), 2.9-2.75 (m, 3H), 2.1-1.9 (m, 3H), 1.7-1.5, (m, 2H), 1.1-1.0 (m, 1H), 0.7-0.6 (m, 2H), 0.45-0.3 (m, 2H); MS:313.

Example 5511-(t-Butyldimethylsilyloxy)-4-(4'-methoxyphenyl)benzene

A solution of 4-bromoanisole (1.87 g, 10 mmol) in dry tetrahydrofuran (20 mL) was cooled to -78°C with stirring under a nitrogen atmosphere. A solution of t-butyl lithium in pentane (1.7 M, 11.8 mL, 20 mmol) was

added dropwise. The reaction mixture was stirred at -78°C for 1 h. A solution of freshly-fused zinc chloride (2.04 g, 15 mmol) in dry tetrahydrofuran (20 mL) was added; the reaction mixture was warmed to 5 -20°C over 20 min, then cooled to -78°C. A solution of 1-bromo-4-t-butyl-dimethylsilyloxybenzene (2.86 g, 10 mmol) in dry tetrahydrofuran (10 mL) was added, followed by tetrakis (triphenylphosphine)palladium (0) (1.15 g, 1 mmol). The reaction was warmed to 50°C and stirred for 10 21 h. The reaction mixture was poured onto a saturated NH₄Cl solution and extracted three times with ethyl acetate. Drying over magnesium sulfate, filtration and removed in vacuo afforded the crude product.

Column chromatography, first with ethyl acetate-hexanes (1:9), then hexanes, afforded the title compound, a solid (2.2 g): ¹H-NMR (CDCl₃, 300 MHz): 7.45 (d, 2H, J=8), 7.4 (d, 2H, J=8), 6.95 (d, 2H, J=8), 6.9 (d, 2H, J=8), 3.85 (s, 3H), 1.0 (s, 9H), 0.25 (s, 6H). The product was still contaminated with trace amounts of 20 triphenylphosphine and starting silyl ether.

Example 552

1-(t-Butyldimethylsilyloxy)-4-(4'-methylthiophenyl)benzene

25 Using the procedure described for Example 551, 4-bromothioanisole (2.03 g, 10 mmol) was converted to the title compound, a solid (0.51 g): ¹H-NMR (CDCl₃, 300 MHz): 7.5 (d, 2H, J=8), 7.45 (d, 2H, J=8), 6.9 (d, 2H, J=8), 6.7 (d, 2H, J=8), 2.5 (s, 3H), 1.0 (s, 9H), 0.2 (s, 6H). This product was also contaminated with 30 triphenylphosphine and starting bromide.

87

Example 5531-(t-Butyldimethylsilyloxy)-4-(4'-fluorophenyl)benzene

Using the procedure described for Example 551, 4-
5 bromofluorobenzene (1.75 g, 10 mmol) was reacted to give
the title compound (2.94 g): $^1\text{H-NMR}$ (CDCl_3 , 300 MHz):
7.5 (dd, 2H, $J=8, 6$), 7.4 (d, 2H, $J=8$), 7.1 (br t, 2H,
 $J=8$), 6.9 (d, 2H, $J=8$), 6.7 (d, 2H, $J=8$), 1.0 (s, 9H),
0.25 (s, 6H). This product was contaminated with
10 triphenylphosphine and starting silyl ether.

Example 554Ethyl-4-(4'-fluorophenyl)benzoate

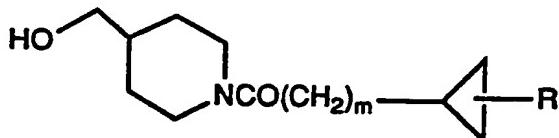
Using the procedure of Example 551, 4-
15 bromofluorobenzene (1.75 g, 10 mmol) was metallated and
coupled with ethyl 4-bromobenzoate (2.28 g, 10 mmol) to
give the title compound after chromatography (ethyl
acetate-hexanes (1:9) (0.7 g)): $^1\text{H-NMR}$ (CDCl_3 , 300 MHz):
8.1 (d, 2H, $J=8$), 7.65-7.5 (m, 4H), 7.15 (t, 2H, $J=8$),
20 4.4 (q, 2H, $J=7$), 1.4 (t, 3H, $J=7$); MS:244.

88

Examples 555 through 557 were prepared according to the methods described for Example 1A (Table 19).

Table 19

5



	<u>Ex.</u>	<u>R</u>	<u>m</u>	<u>bp (°C)</u>
10	555	2-CH ₃	0	145-150 (0.5 mm Hg) (a)
	556	2,2-Cl ₂ -1-CH ₃	0	(b)
	557	H	1	145-150 (0.2 mm Hg) (c)

Footnotes for Table 19

- (a) ¹H-NMR (CDCl₃, 300 MHz): 4.7-4.5 (m, 1H), 4.3-4.1 (m, 1H), 3.6-3.4 (m, 2H), 3.1 (br t, 1H, J=7), 2.6 (br t, 1H, J=7), 2.0-1.6 (m, 5H), 1.5-1.0 (m, 4H), 1.1 (d, 3H, J=7), 0.65-0.55 (m, 1H); MS:197.
- (b) mp=105-107°C; ¹H-NMR (CDCl₃, 300 MHz): 4.6 (br t, 1H, J=7), 3.95 (br t, 1H, J=7), 3.6-3.5 (m, 2H), 3.25 (m, 1H), 2.8-2.6 (m, 1H), 2.1-1.7 (m, 6H), 1.55 (d, 3H, J=7), 1.5-1.1 (m, 2H); MS:265.
- (c) ¹H-NMR (CDCl₃, 300 MHz): 4.65 (br d, 1H, J=10), 3.9 (br d, 1H, J=10), 3.55-3.45 (m, 2H), 3.1-2.9 (m, 2H), 2.65-2.5 (m, 1H), 2.3 (d, 2H, J=7), 2.0-1.6 (m, 4H), 1.3-1.0 (m, 4H).

Utilities Section

The compounds of this invention and their pharmaceutically acceptable salts possess psychotropic properties, particularly antipsychotic activity of good duration with selective sigma receptor antagonist activities while lacking the typical movement disorder side-effects of standard dopamine receptor antagonist

antipsychotic agents. These compounds may also be useful as antidotes for certain psychotomimetic agents such as phencyclidine (PCP), and as antidyskinetic agents.

5

In vitro

Sigma Receptor Binding Assay

Male Hartley guinea pigs (250-300 g, Charles River) were sacrificed by decapitation. Brain membranes were 10 prepared by the method of Tam (Proc. Natl. Acad. Sci. USA 80: 6703-6707, 1983). Whole brains were homogenized (20 seconds) in 10 vol (wt/vol) of ice-cold 0.34 M sucrose with a Brinkmann Polytron (setting 8). The homogenate was centrifuged at 920 x g for 10 minutes. 15 The supernatant was centrifuged at 47,000 x g for 20 minutes. The resulting membrane pellet was resuspended in 10 vol (original wt/vol) of 50 mM Tris HCl (pH 7.4) and incubated at 37°C for 45 minutes to degrade and dissociate bound endogenous ligands. The membranes were 20 then centrifuged at 47,000 x g for 20 minutes and resuspended in 50 mM Tris HCl (50 mL per brain).

0.5 mL aliquots of the membrane preparation were incubated with unlabeled drugs, 1 nM (+)-[³H]SKF 10,047 in 50 mM Tris HCl, pH 7.4, in a final volume of 1 mL. 25 Nonspecific binding was measured in the presence of 10 μM (+)-SKF 10,047. The apparent dissociation constant (K_d) for (+)-[³H]SKF 10,047 is 50 nM. After 45 minutes of incubation at room temperature, samples were filtered rapidly through Whatman GF/C glass filters under 30 negative pressure, and washed 3 times with ice-cold Tris buffer (5 mL).

IC_{50} s were calculated from log-logit plots. Apparent K_i 's were calculated from the equation, $K_i = IC_{50}/[1 + (L/K_d)]$ (4), where L is the concentration of

90

radioligand and K_d is its dissociation constant. Data are shown in Table I.

Dopamine Receptor Binding

5 Membranes were prepared from guinea pig striatum by the method described for sigma receptor binding. The membranes were then resuspended in 50 mM Tris HCl (9 mL per brain).

10 0.5 mL aliquots of the membrane preparation were 10 incubated with unlabeled drugs, and 0.15 nM [3 H]spiperone in a final volume of 1 mL containing 50 mM Tris HCl, 120 mM NaCl and 1 mM MgCl₂ (pH 7.7).

15 Nonspecific binding was measured in the presence of 100 nM (+)-butaclamol. After 15 minutes of incubation at 37°C, samples were filtered rapidly through Whatman GF/C glass filters under negative pressure, and washed three times with ice-cold binding buffer (5 mL).

IC₅₀s were calculated from log-logit plots.

20 Apparent K_i s were calculated from the equation $K_i = IC_{50} [1 + (L/K_d)]$ (4), where L is the concentration of radioligand and K_d is its dissociation constant. Data are shown in Table I.

25 The data in Table I indicate that haloperidol, a typical antipsychotic drug, has potent binding affinity for both the sigma and dopamine receptors. This binding profile of haloperidol reflects the therapeutic activity as well as the motor side effects caused by antagonism of the dopamine receptors. In contrast, the examples of this invention shown in Table I indicate potent and 30 selective binding affinity for sigma receptors without binding to the dopamine receptors. Therefore these compounds are not expected to produce the extrapyramidal symptoms that are typical of that produced by haloperidol and other typical antipsychotics that are 35 dopamine receptor antagonists.

In VivoIsolation-Induced Aggression in Mice

This is a modification of the method of Yen et al.
5 (Arch. Int. Pharmacodyn. 123: 179-185, 1959) and Jannsen
et al. (J. Pharmacol. Exp. Ther. 129: 471-475, 1960).
Male Balb/c mice (Charles River) were used. After 2
weeks of isolation in plastic cages (11.5 x 5.75 x 6 in)
the mice were selected for aggression by placing a
10 normal group-housed mouse in the cage with the isolate
for a maximum of 3 minutes. Isolated mice failing to
consistently attack an intruder were eliminated from the
colony.

Drug testing was carried out by treating the
15 isolated mice with test drugs or standards. Fifteen
minutes after dosing with test drugs by the oral route,
one isolated mouse was removed from its home cage and
placed in the home cage of another isolate. Scoring was
a yes or no response for each pair. A maximum of 3
20 minutes was allowed for an attack and the pair was
separated immediately upon an attack. Selection of home
cage and intruder mice was randomized for each test.
Mice were treated and tested twice a week with at least
a 2 day washout period between treatments.
25 As shown in Table II, haloperidol and Examples 1,
228, 409, 493 and 494 all have potent activities in
inhibiting the isolation-induced aggressive behavior
indicating psychotropic activities.

30 PCP-Induced Turning Behavior in Rats

Male Sprague-Dawley rats (CD/CR, Charles River),
weighing 190-290 g, were used for surgery. In order to
spare nonadrenergic neurons, rats were injected with 25
mg/kg imipramine i.p. 30 minutes before surgery. The
35 rats were anesthetized with a 1:1.2 ratio mixture of

Xylazine:Ketamine given 0.1 mL/100 g body weight i.m. A Ringers-Wydaze (100:0.01) solution was given to prevent dehydration. Dopamine was depleted in the right striatum by injecting the neurotoxin 6-hydroxydopamine 5 (6-OHDA) into the substantia nigra of the right cerebral hemisphere. Five mg of 6-OHDA was dissolved in 5 mL of a 0.04% ascorbic acid solution which had been deoxygenated with nitrogen. Five μ L of the 6-OHDA solution was injected into the substantia nigra through 10 a 26 gauge needle over a five minute period.

Stereotaxic injection coordinates were -2.5 mm posterior to bregma, -2.1 mm right of the midsagittal suture, and -8.6 mm below the skull surface with the incisor bar set at +5.0 mm. Following surgery they were given 10 days 15 to recover while housed four per cage (45.0 L x 20.0 H x 26.0 W) with ALPHA-dri bedding and ad lib access to Pro-Lab rodent chow and deionized water. Following recovery, the wood clips were removed, the rats were individually housed in suspended cages, and they were 20 placed on a restricted diet so that their weight did not exceed 375 g. At all times they were housed in the animal care facility under a 12-12 hour light/dark cycle (light on at 6:00 h, light off at 18:00 h).

Rotation rate and direction were determined with 25 Coulbourn Instruments Rotometry Monitors. Clockwise and counter clockwise rotations were recorded at 30 and 60 minute intervals. The rats were examined for correct lesion location by testing for rotational activity induced by s.c. injections of 3.0 mg/kg D-amphetamine 30 SO₄, and 2.0 mg/kg PCP HCl, respectively. These drugs were administered in the following sequence: Amphetamine was given 30 second before testing. Seven days later, the rats were injected with PCP 30 seconds before testing. Only those rats with an ipsilateral rotation

rate of 2.5 turns per minute or higher were used in subsequent tests.

Methocel® or test drugs were administered by the oral route (p.o.) 20 minutes before testing.

- 5 Phencyclidine (1.5 mg/kg) was given s.c. immediately before testing.

The data were analyzed with an analysis of variance statistical test and individual comparisons of each dose of test drug to control were made with Dunnett's 10 multiple range test. The ED50 was calculated with a Litchfield and Wilcoxon test using percent of control values. Data are shown in Table III.

Induction of Catalepsy

15 This is a modification of the method of Costall and Naylor (Psychopharmacologia (Berl.), 43, 69-74, 1975). Male CD rats (Charles River) weighing 250-300 g were treated with test drugs and standards by the oral route and tested for the presence of catalepsy 30 minute, 60 20 minute, and 90 minute after treatment. To test for catalepsy, each rat is placed with its front paws over a 10 cm high horizontal bar. The intensity of catalepsy is measured by the length of time it takes the animal to move both forelegs to the table. A time of 20 seconds is 25 considered maximal catalepsy. Data is shown in Table III.

As shown in Table III, both haloperidol and Example 494 have potent activity in inhibiting the potent hallucinogen PCP-induced turning behavior in rats, supporting their use for treatment of psychosis. In the 30 catalepsy test which is a model for extrapyramidal symptoms, haloperidol is very potent in producing catalepsy and this agrees well with the side-effect profile of haloperidol in the clinic. In contrast, Example 494 does not produce catalepsy and suggests very low potential for 35 extrapyramidal symptoms and tardive dyskinesia.

94

Table I

Receptor Binding Affinity

<u>Example</u>	<u>Sigma</u>	<u>(D-2)</u>
Haloperidol	+++	+++
5 1	+++	-
230	+++	-
233	++	-
234	+++	-
240	++	-
10 411	+++	-
412	+++	-
413	++	-
416	+++	-
435	+++	-
15 442	++	-
504	+++	-
505	++	-
506	++	-
544	++	-
20 539	+	-
541	++	-
542	+++	-
543	+	-
547	+++	-
25 548	+++	+
545	+	-
546	+++	-
549	+	-
420	+++	-
30 421	+++	-
422	++	-
423	+++	-
323	+	-
326	++	-

95

Table I (continued)

Receptor Binding Affinity

	<u>Example</u>	<u>Sigma</u>	<u>(D-2)</u>
	424	+++	+
5	425	+++	-
	525	+++	+
	515	+++	
	516	+++	-
	511	+	-
10	509	+++	-
	533	+	-
	532	++	-
	530	+++	-

15

Table II

In Vivo

Inhibition of

Isolation-induced Aggression

	<u>Example</u>	
	Haloperidol	+++
20	1	++
	230	+++
	411	+
	503	+++
	504	+++

25

Table III

In Vivo

Inhibition of

PCP-induced

	<u>Example</u>	<u>Turning</u>	<u>Catalepsy</u>
	Haloperidol	+++	+++
	504	+++	-

Dosage Forms

Daily dosage ranges from 1 mg to 2000 mg. Dosage forms (compositions) suitable for administration ordinarily will contain 0.5-95% by weight of the active 5 ingredient based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, 10 syrups, and suspensions; it can also be administered parenterally in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, sucrose, mannitol, starch, cellulose derivatives, magnesium stearate, 15 stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and 20 protect the tablet from the atmosphere, or enteric-coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient 25 acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions.

Solutions for parenteral administration preferably 30 contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either 35 alone or combined, are suitable stabilizing agents.

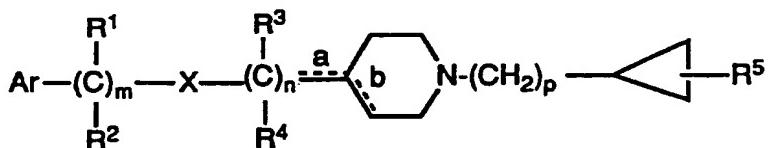
97

Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

- 5 Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in this field.

WHAT IS CLAIMED IS:

1. A compound having the formula:



5

(I)

or a pharmaceutically acceptable salt thereof, wherein:

m is 0 to 3;

n is 0 to 3;

10 provided m and n are not both 0;

p is 0 to 3;

X is O, S, SO, SO₂, NR⁶, CR⁷R⁸, CO, or CHO;

15 R¹, R³, and R⁷ independently are H, alkyl of 1 to 5 carbon atoms, halogen, NR¹⁰R¹¹, OH, CO₂H,

carboalkoxy of 2 to 6 carbon atoms, CN, Ar¹, alkoxy of 1 to 5 carbon atoms or alkylthio of 1 to 5 carbon atoms;

20 R², R⁴ and R⁸ independently are H, alkyl of 1 to 5 carbon atoms, carboalkoxy of 2 to 6 carbon atoms,

CN, alkoxy of 1 to 5 carbon atoms or Ar¹;

provided that R¹, R², R³ and R⁴ are not alkoxy of 1 to 5 carbon atoms, alkylthio of 1 to 5 carbon atoms, NR¹⁰R¹¹ or OH when X is O, S, SO, SO₂ or NR⁶;

25 R⁵ is H, alkyl, halogen, OH or alkenyl;

R⁶ is H, alkyl of 1 to 5 carbon atoms or Ar¹;

Ar and Ar¹ independently are naphthyl, pyridyl, pyrimidyl, indolyl, quinolinyl, isoquinolinyl, or phenyl optionally substituted with

alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3

30 carbon atoms, haloalkyl of 1 to 3 carbon atoms and 1 to 7 halogen atoms, SH, S(O)_t alkyl of 1 to 3 carbon atoms, where t is 1, 2 or 3, dialkylamino

of 2 to 6 carbon atoms, halogen, OH, alkylamino of 1 to 3 carbon atoms, NH₂, CN, NO₂, SO₃H, tetrazole, CO₂H, carboalkoxy of 2 to 6 carbon atoms, CONH₂, SO₂NH₂, COR⁹, CONR¹²R¹³, SO₂NR¹²R¹³,

5 Ar², OAr² or SAr²;

Ar² is naphthyl or phenyl optionally substituted with alkyl of 1 to 3 carbon atoms, haloalkyl of 1 to 3 carbon atoms and 1 to 7 halogen atoms, alkoxy of 1 to 3 carbon atoms, halogen or alkylthio of 1 to 3

10 carbon atoms;

R⁹, R¹⁰, R¹¹, R¹² and R¹³ independently are H, alkyl of 1 to 5 carbon atoms or phenyl or R¹⁰ and R¹¹ taken together are an alkylene chain of 3 to 6 carbon atoms or R¹² and R¹³ taken together are an alkylene

15 chain of 3 to 6 carbon atoms; and

a or b is a double bond or a single bond, provided that both are not double bonds.

2. A compound of Claim 1 wherein X is CO, O or CHO.

3. A compound of Claim 1 wherein m is 0.

20 4. A compound of Claim 1 wherein n and p are each 1.

5. A compound of Claim 1 wherein R³-R⁵ are H.

6. A compound of Claim 1 wherein Ar is phenyl optionally substituted with halogen, OCH₃, NH₂, NO₂ or another phenyl group.

25 7. A compound of Claim 1 wherein:

X is CO, O, CHO;

m is 0;

n and p are each 1;

R³-R⁵ are H; and

30 Ar is phenyl optionally substituted with halogen, OCH₃, NH₂, NO₂ or another phenyl group.

8. A compound of Claim 7 wherein X is CO.

9. A compound of Claim 7 wherein Ar is 4-fluorophenyl.

10. A compound of Claim 7 wherein:

35 X is CO;

100

n and p are each 1;
R³, R⁴ and R⁵ are H; and
Ar is 4-fluorophenyl.

11. A compound of Claim 7 wherein X is O.
- 5 12. A compound of Claim 7 wherein:
X is O;
m is O;
n and p are each 1;
R³, R⁴ and R⁵ are H; and
10 Ar is 4-fluorophenyl.
13. The compound of Claim 1 which is 1-(cyclopropylmethyl)-4-(2'-(4"-fluorophenyl)-2'-oxoethyl)piperidine.
14. The compound of Claim 1 which is 1-(cyclopropylmethyl)-4-(2'-(4"-fluorophenyl)-2'-oxoethyl)piperidine, hydrobromide salt.
- 15 15. The compound of Claim 1 which is 1-(cyclopropylmethyl)-4-(2'-(4"-chlorophenyl)-2'-oxoethyl)piperidine.
16. The compound of Claim 1 which is 1-(cyclopropylmethyl)-4-(2'-(4"-chlorophenyl)-2'-oxoethyl)piperidine, hydrobromide salt.
- 20 17. The compound of Claim 1 which is 1-(cyclopropylmethyl)-4-(4'-fluorophenoxyethyl)piperidine.
18. The compound of Claim 1 which is 1-(cyclopropylmethyl)-4-(4'-fluorophenoxyethyl)piperidine, hydrochloride salt.
- 25 19. The compound of Claim 1 which is 1-(cyclopropylmethyl)-4-(4'-chlorophenoxy-methyl)piperidine.
20. The compound of Claim 1 which is 1-(cyclopropylmethyl)-4-(4'-chlorophenoxy-methyl)piperidine, hydrochloride salt.

101

21. The compound of Claim 1 which is 1-(cyclopropylmethyl)-4-(4'-nitrophenoxyethyl)piperidine.
22. The compound of Claim 1 which is 1-(cyclopropylmethyl)-4-(2'-(4''-biphenyl)-2'-oxoethyl)piperidine.
23. The compound of Claim 1 which is 1-(cyclopropylmethyl)-4-(2'-(4''-biphenyl)-2'-oxoethyl)piperidine, hydrobromide salt.
- 10 24. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an antipsychotic effective amount of a compound of Claim 1.
- 15 25. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an antipsychotic effective amount of a compound of Claim 2.
- 20 26. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an antipsychotic effective amount of a compound of Claim 3.
- 25 27. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an antipsychotic effective amount of a compound of Claim 4.
- 30 28. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an antipsychotic effective amount of a compound of Claim 5.
- 30 29. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an antipsychotic effective amount of a compound of Claim 6.
- 35 30. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an

102

- antipsychotic effective amount of a compound of
Claim 7.
31. A pharmaceutical composition comprising a
pharmaceutically acceptable carrier and an
5 antipsychotic effective amount of a compound of
Claim 8.
32. A pharmaceutical composition comprising a
pharmaceutically acceptable carrier and an
antipsychotic effective amount of a compound of
10 Claim 9.
33. A pharmaceutical composition comprising a
pharmaceutically acceptable carrier and an
antipsychotic effective amount of a compound of
Claim 10.
- 15 34. A pharmaceutical composition comprising a
pharmaceutically acceptable carrier and an
antipsychotic effective amount of a compound of
Claim 11.
35. A pharmaceutical composition comprising a
20 pharmaceutically acceptable carrier and an
antipsychotic effective amount of a compound of
Claim 12.
36. A pharmaceutical composition comprising a
pharmaceutically acceptable carrier and an
25 antipsychotic effective amount of the compound of
Claim 13.
37. A pharmaceutical composition comprising a
pharmaceutically acceptable carrier and an
antipsychotic effective amount of the compound of
30 Claim 14.
38. A pharmaceutical composition comprising a
pharmaceutically acceptable carrier and an
antipsychotic effective amount of the compound of
Claim 15.

103

39. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an antipsychotic effective amount of the compound of Claim 16.
- 5 40. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an antipsychotic effective amount of the compound of Claim 17.
- 10 41. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an antipsychotic effective amount of the compound of Claim 18.
- 15 42. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an antipsychotic effective amount of the compound of Claim 19.
- 20 43. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an antipsychotic effective amount of the compound of Claim 20.
- 25 44. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an antipsychotic effective amount of the compound of Claim 21.
- 30 45. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an antipsychotic effective amount of the compound of Claim 22.
- 35 46. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an antipsychotic effective amount of the compound of Claim 23.
47. A method of treating physiological or drug induced psychosis or dyskinesia in a mammal comprising administering to the mammal an antipsychotic or

104

- antidyskinetic effective amount of a compound of
Claim 1.
48. A method of treating physiological or drug induced
psychosis or dyskinesia in a mammal comprising
5 administering to the mammal an antipsychotic or
antidyskinetic effective amount of a compound of
Claim 2.
49. A method of treating physiological or drug induced
psychosis or dyskinesia in a mammal comprising
10 administering to the mammal an antipsychotic or
antidyskinetic effective amount of a compound of
Claim 3.
50. A method of treating physiological or drug induced
psychosis or dyskinesia in a mammal comprising
15 administering to the mammal an antipsychotic or
antidyskinetic effective amount of a compound of
Claim 4.
51. A method of treating physiological or drug induced
psychosis or dyskinesia in a mammal comprising
20 administering to the mammal an antipsychotic or
antidyskinetic effective amount of a compound of
Claim 5.
52. A method of treating physiological or drug induced
psychosis or dyskinesia in a mammal comprising
25 administering to the mammal an antipsychotic or
antidyskinetic effective amount of a compound of
Claim 6.
53. A method of treating physiological or drug induced
psychosis or dyskinesia in a mammal comprising
30 administering to the mammal an antipsychotic or
antidyskinetic effective amount of a compound of
Claim 7.
54. A method of treating physiological or drug induced
psychosis or dyskinesia in a mammal comprising
35 administering to the mammal an antipsychotic or

- antidyskinetic effective amount of a compound of
Claim 8.
55. A method of treating physiological or drug induced
psychosis or dyskinesia in a mammal comprising
5 administering to the mammal an antipsychotic or
antidyskinetic effective amount of a compound of
Claim 9.
56. A method of treating physiological or drug induced
psychosis or dyskinesia in a mammal comprising
10 administering to the mammal an antipsychotic or
antidyskinetic effective amount of a compound of
Claim 10.
57. A method of treating physiological or drug induced
psychosis or dyskinesia in a mammal comprising
15 administering to the mammal an antipsychotic or
antidyskinetic effective amount of a compound of
Claim 11.
58. A method of treating physiological or drug induced
psychosis or dyskinesia in a mammal comprising
20 administering to the mammal an antipsychotic or
antidyskinetic effective amount of a compound of
Claim 12.
59. A method of treating physiological or drug induced
psychosis or dyskinesia in a mammal comprising
25 administering to the mammal an antipsychotic or
antidyskinetic effective amount of the compound of
Claim 13.
60. A method of treating physiological or drug induced
psychosis or dyskinesia in a mammal comprising
30 administering to the mammal an antipsychotic or
antidyskinetic effective amount of the compound of
Claim 14.
61. A method of treating physiological or drug induced
psychosis or dyskinesia in a mammal comprising
35 administering to the mammal an antipsychotic or

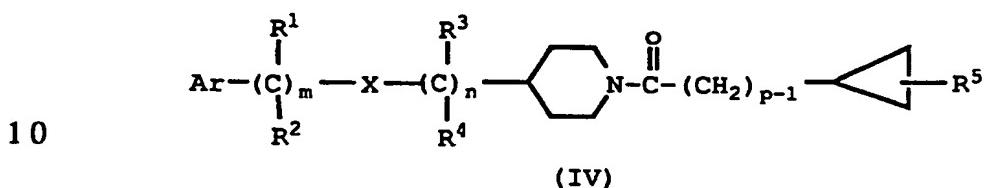
106

- antidyskinetic effective amount of the compound of
Claim 15.
62. A method of treating physiological or drug induced
psychosis or dyskinesia in a mammal comprising
5 administering to the mammal an antipsychotic or
antidyskinetic effective amount of the compound of
Claim 16.
63. A method of treating physiological or drug induced
psychosis or dyskinesia in a mammal comprising
10 administering to the mammal an antipsychotic or
antidyskinetic effective amount of the compound of
Claim 17.
64. A method of treating physiological or drug induced
psychosis or dyskinesia in a mammal comprising
15 administering to the mammal an antipsychotic or
antidyskinetic effective amount of the compound of
Claim 18.
65. A method of treating physiological or drug induced
psychosis or dyskinesia in a mammal comprising
20 administering to the mammal an antipsychotic or
antidyskinetic effective amount of the compound of
Claim 19.
66. A method of treating physiological or drug induced
psychosis or dyskinesia in a mammal comprising
25 administering to the mammal an antipsychotic or
antidyskinetic effective amount of the compound of
Claim 20.
67. A method of treating physiological or drug induced
psychosis or dyskinesia in a mammal comprising
30 administering to the mammal an antipsychotic or
antidyskinetic effective amount of the compound of
Claim 21.
68. A method of treating physiological or drug induced
psychosis or dyskinesia in a mammal comprising
35 administering to the mammal an antipsychotic or

antidyskinetic effective amount of the compound of Claim 22.

69. A method of treating physiological or drug induced psychosis or dyskinesia in a mammal comprising administering to the mammal an antipsychotic or antidyskinetic effective amount of the compound of Claim 23.

- 5 70. A compound having the formula:



wherein:

m is 0 to 3;

n is 0 to 3;

15 provided that m and n are not both 0;

p is 1 to 3;

X is O, S, NR⁶;

20 Ar and Ar¹ independently are naphthyl, pyridyl, pyrimidyl, quinolinyl, isoquinolinyl or phenyl optionally substituted with

alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, haloalkyl of 1 to 3 carbon atoms and 1 to 7 halogen atoms, S(O)_t alkyl of 1 to 3 carbon atoms, where t is 1, 2 or 3, dialkylamino of 2 to 6 carbon atoms, halogen, alkylamino of 1 to 3 carbon atoms, CN, NO₂, carboalkoxy of 2 to 6 carbon atoms, COR⁹, CONR¹²R¹³, SO₂NR¹²R¹³ Ar², OAr² or SAR²;

25 30 Ar² is naphthyl or phenyl optionally substituted with alkyl of 1 to 3 carbon atoms, haloalkyl of 1 to 3 carbon atoms and 1 to 7 halogen

108

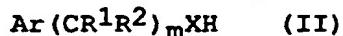
atoms, alkoxy of 1 to 3 carbon atoms, halogen or alkylthio of 1 to 3 carbon atoms;

R¹-R⁴ and R⁶ independently are H, alkyl of 1 to 5 carbon atoms or Ar¹;

5 R⁵ is H, alkyl, halogen, OH or alkenyl; and R⁹, R¹² and R¹³ independently are H, alkyl of 1 to 5 carbon atoms or phenyl, or R¹² and R¹³ taken together are an alkylene chain of 3 to 6 carbon atoms.

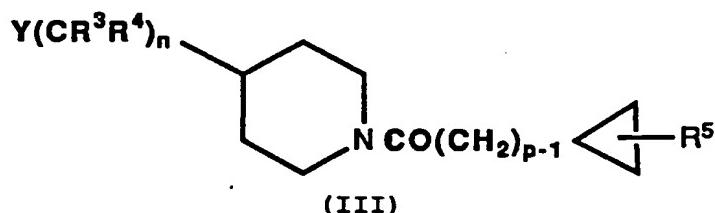
10 71. A process for preparing the compounds of Formula (IV) comprising

(a) reacting a compound of the formula:



where: X is O, S, NR⁶ or CH₂ when m is 1 and CR¹R² is CO;

15 (b) with a compound of the Formula:

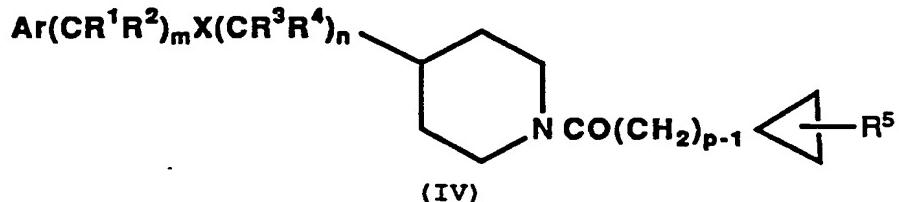


20

where: Y is halide, arylsulfonyloxy, alkylsulfonyloxy, haloalkylsulfonyloxy or acyloxy;

25

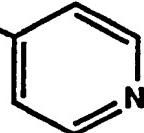
in the presence of a base and an inert solvent; providing a compound of Formula:



109

72. A process for preparing the compounds of Formula (I) where X is O, S, CHO or NR⁶ comprising reducing a compound of Formula (IV), prepared by the process of Claim 71, with a reducing agent in an inert solvent.

- 5 73. A process for preparing the compounds of Formula (I) where X is CO or CHO comprising
 (a) treating a compound of formula:



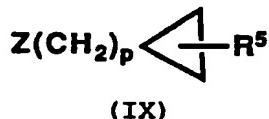
10

(VIII)

where:

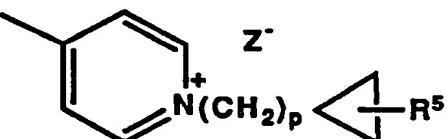
with an alkylating agent of the formula:

15



20

where: Z is halogen, arylsulfonyloxy or haloalkylsulfonyloxy to form a compound of the formula:

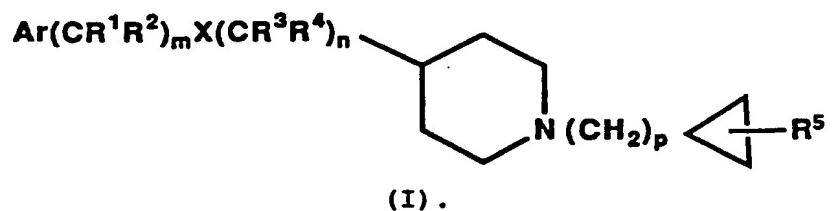


and

25

- (b) reducing the resulting compound of formula (X) to provide a compound of the formula:

110



INTERNATIONAL SEARCH REPORT

International Application No PCT/US90/04850

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ³		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC(5): A61K 31/445; C07D 211/30, 20		
U.S. CL.: 514/317, 546/225, 236		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁴		
Classification System	Classification Symbols	
U.S.	514/317; 546/225, 236	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁵		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴		
Category [*]	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
Y	US, A, 4,294,841 (CHAMPSEIX ET AL.) 13 October 1981. See the entire document.	1 to 70, 72
Y	Journal of Medicinal Chemistry, volume 15, No. 6, 1972, IRWIN ET AL., "Alkyl Derivatives of Tetrahydroisoquinoline, 1-Phenylpiperazine, and 4-DiphenylmethylPIPERIDINE", see pages 690 to 692.	1 to 70
Y	Chemical Abstracts, Volume 95, 1981, EISTETTER ET AL., "4-Phenoxyppiperidines, their use and medicaments containing them", abstract No. 24830h.	1 to 70, 72
Y	Chemical Abstracts, Volume 96, 1982, TRIJZELAAR ET AL., "Quinoline derivatives, their use, pharmaceutical compositions containing them and a method for the preparation of these pharmaceutical compositions", Abstract No. 123074S.	1 to 70
Y	US, A, 4,243,807 (FRIEBE ET AL.) 06 January 1981. See the entire document.	71
Y	US, A, 4,783471 (CARR ET AL.) 08 November 1988. See pages 1 and 2.	73
A	US, A, 4,593,037 (SARGES) 03 June 1986. See entire document.	
<p>[*] Special categories of cited documents: ¹⁶ "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed</p> <p>^{"T"} later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention ^{"X"} document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step ^{"Y"} document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. ^{"A"} document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search ¹⁹	Date of Mailing of this International Search Report ²⁰	
20 NOVEMBER 1990	28 JAN 1991	
International Searching Authority ¹	Signature of Authorized Officer	
ISA/US	NGUYEN NGOC-HO BA K. TRINH INTERNATIONAL DIVISION	

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.